The New England
Journal of Medicine

Copyright, 1943, by the Massachusetts Medical Society

Volume 229 NOVEMBER 11, 1943 Number 20

ENDOCRINE AND PSEUDOENDOCRINE PROBLEMS IN CHILDHOOD*

Richard Wagner, M.D.†

BOSTON

RIGHTFULLY endocrine and pseudoendocrine problems in childhood deserve consideration together. Many anomalies and disturbances of growth and development and certain cases of retarded sexual development, of an abnormal accumulation and distribution of fat, of dwarfism and even of mental retardation are often mistakenly grouped as the expression of an endocrine imbalance. There are many more, and to a certain extent more important, problems that are often considered as endocrinopathies but that have only a very loose relation, or no relation at all, to a disturbance of one of the hormone glands. Regarding true endocrinopathies that are of importance in general pediatric practice, if one were to count them on the fingers of both hands, there would certainly be quite a few fingers left over.

There are three large groups of diseases and anomalies that have certain features in common but that differ from each other by their etiology as well as by the dominance of certain characteristics. These characteristics determine the condition in question and classify it under the heading of one of these three groups, which are as follows:

Group 1. True endocrine disorders caused by a pathologic process or anomaly of an endocrine gland, which may be even a congenital absence.

Group 2. Accentuations of physiologic phases of development, which sometimes imitate true endocrinopathies. Constitutional and familial factors are frequently involved. Transitory states, such as transitory infantilism, certain forms of obesity and disharmonic development, should be included.

Group 3. Congenital anomalies and multiple deviations, retardation of development, somatic as well as mental, sometimes mistaken for endocrinopathies and showing some of their essential features. Not infrequently they overlap. This group should properly be called genopathies rather than endocrinopathies.

When dealing with a possible endocrine disorder in childhood, certain routine measures should be carried out so that the condition may be more accurately classified. The following is a brief outline of such a scheme:

Exact body measurements (standing and sitting height, circumferences of head and chest, breadths of chest and pelvis, and span); appraisal of proportions (stem index); velocity of growth and relative growth rate when the patient is observed over a longer period of time.

Determination of the bone age by x-ray; eventually, x-ray examination of teeth and skull.

Appraisal of the genital and extragenital characteristics.

Examination of eyegrounds and visual fields.

Laboratory tests appropriate to the given case, such as basal metabolic rate, specific dynamic action, sugar-tolerance test (glucose or galactose), determination of blood cholesterol and cholesterol ester levels, and assays of sex hormones in the urine and follicle-stimulating hormone in the blood. (Certain laboratory tests are important only for selected cases, such as the insulin-tolerance test and the dextrose-insulin tolerance test in the diagnosis of endocrinologic disorders of dextrose metabolism, and determination of the sodium and potassium levels in cases of possible suprarenal involvement.)

Psychometric tests.

Accurate records of response to treatment.

In the physical examination, special attention should be given to hematologic studies (hypochromic anemia in myxedema), the heart and electrocardiogram (characteristic changes in hyperthyroidism and hypothyroidism), the blood pressure (elevation in adrenocortical obesity with macrogenitosomia) and the size of the liver (hep-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

From the Department of Pediatrics, Tufts College Medical School, the Boston Floating Hospital and the Children's Department, Boston Dispensary.

†Assistant professor of pediatrics, Tufts College Medical School; physician, Boston Floating Hospital.

atomegaly in dwarfism due to glycogenesis). All cases should be examined from the point of view of somatic stigmas, according to a certain schedule, which space does not permit discussing in detail here. Of particular interest is the mesenchymatous group of stigmas, such as curved fifth finger, brachydactylia, fusion and other anomalies of the ribs, malocclusion, ear nodules and so forth — not only their presence but also their occurrence together.

To illustrate Group 1, the true endocrinopathies, I shall select only two examples — congenital cretinism and pituitary dwarfism.

Figure 1 shows a case of congenital cretinism in a child of five weeks with all the characteristic signs. Early diagnosis and treatment are essential

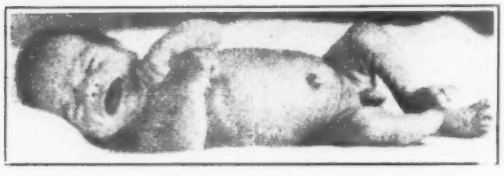


FIGURE 1. *Congenital Cretinism in a Five-Week-Old Baby (Nobel et al.[1]).*

The photograph shows the characteristic facies, the macroglossia and an umbilical hernia.

in order to prevent further progressive stages of deterioration, which are never completely reparable, as is demonstrated in Figure 2. Even if the somatic development shows good progress, as illustrated by the improvement of skeletal development under the influence of thyroid treatment, the end result is poor so far as mental development is concerned.

The next example is concerned with pituitary dwarfism. Many mistakes are still made in the diagnosis, although it is usually quite simple. Figure 3 shows a pituitary dwarf of fourteen years. The only obligatory clinical signs are dwarfism and complete failure of sexual development if the condition has an onset during the early period of childhood, or atrophy of the genitalia if these have developed before the onset of the condition. The lack of mental retardation is important. All the other signs and symptoms, such as obesity, geroderma and diabetes insipidus, and many of the laboratory findings are nonobligatory for the diagnosis. Changes of the eyegrounds and visual fields may or may not be present, depending on the site of the lesion and the duration of the process. The underlying lesion in the case shown in Figure 3 was a cystic tumor of the hypophyseal duct, consisting of squamous epithelium. The same picture may be observed without the presence of a tumor. The primary deficiency in pituitary dwarfism may be the result of congenital absence of the acidophilic cells, surgical ablation, pressure necrosis, infection, infarction, calcification or any destructive lesion in or in the immediate vicinity of the gland. The midbrain is sometimes involved,

FIGURE 2. *Congenital Cretinism in a Seventeen-Year-Old Girl (Nobel et al.[1]).*

Before treatment (photographs on left), the height and bone age corresponded to those of a child of one and a half years. After seventeen months of thyroid treatment (photographs on right), the height had increased 18 cm. and there was striking progress in skeletal development.

with repercussion on the gland. One of the youngest cases on record is now under observation at the Boston Floating Hospital and the Boston Dispensary (Fig. 4).

The treatment of pituitary dwarfism consists of surgical removal of an existing tumor and of hormone therapy in the other cases. Methyltestosterone, which is given by mouth, is the best of the preparations available at this time for the hormone treatment of pituitary dwarfism (Fig. 5). It is a specific factor stimulating linear growth and the interstitial tissue of the gonads. The drug stimulates the development of the secondary sexual characteristics but has no influence on the maturing process of the gonads proper. It does not stimulate spermatogenesis and therefore does not lead to early closure of the epiphyses. Only completed sexual maturity arrests skeletal growth and leads to the fusion of the epiphyses. The growth-

stimulating effect of testosterone derivatives in hypogonadal subjects has been studied by several investigators (Moricard and Bize,[4] Villaret, Justin-Besançon and Rubens-Duval,[5] Webster,[6] Webster and Hoskins,[7] and Browne and Ross[8]). The introduction of a methyl radical greatly enhanced the peroral effects of testosterone, as shown by Miescher and Tschopp.[9]

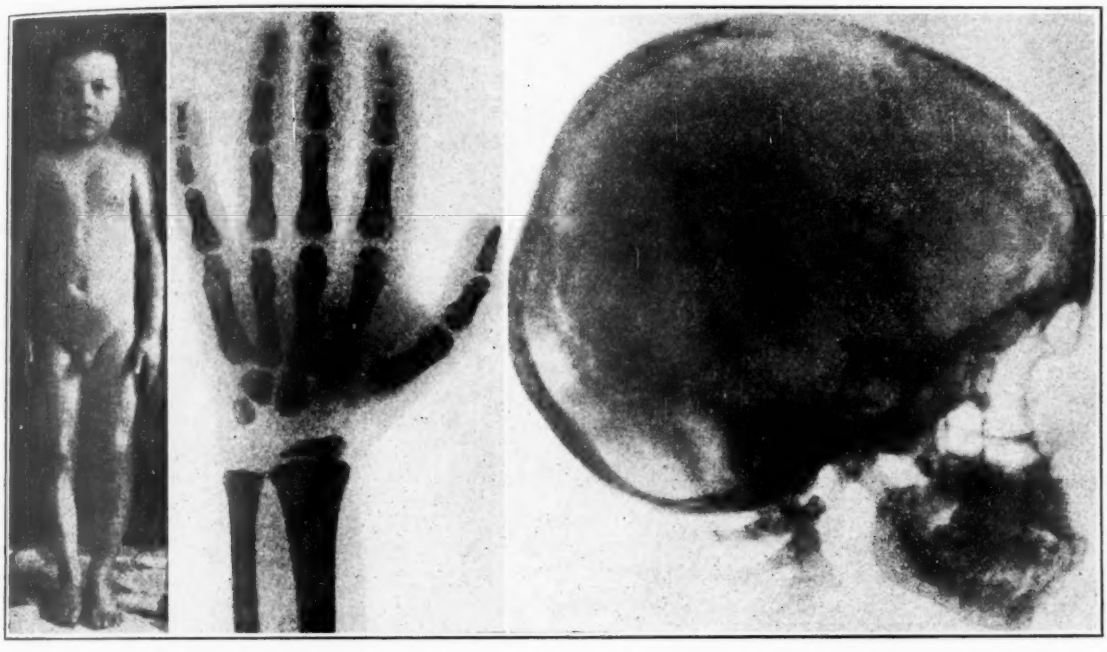


FIGURE 3. *Pituitary Dwarfism in a Fourteen-Year-Old Boy (Nobel et al.[1]).*

The height was only 107 cm., corresponding to that of a child of five and a half years. The bone age was consistent with that of a child of three years. The testicles were atrophied, and there was atrophy of the optic nerve, with temporal hemianopia. The x-ray film of the skull shows a suprasellar cyst and increased convolutional markings.

Pituitary hormones and the chorionic gonadotropins are on the whole a disappointment so far as the treatment of pituitary dwarfism is concerned. So long as there are no synthetic hormones available, as, for example, in the case of the sex hormones, but only crude extracts, the therapeutic results are doubtful and not consistent. On the other hand, in some supposedly hypopituitary conditions — for example, in certain selected cases of cryptorchidism — treatment with chorionic gonadotropins is valuable.

In the differential diagnosis between panhypopituitarism and male eunuchoidism the 17-ketosteroid assay and that of the follicle-stimulating hormone test in the urine have recently become of great importance. According to Fraser, Forbes, Albright, Sulkowitch and Reifenstein,[10] patients with panhypopituitarism have no 17-ketosteroids or very low assays. Cases of male eunuchoidism are divided into two groups, those giving positive and those giving negative follicle-stimulating hormone tests with the urine. The cases in the latter group exhibit a rise in the 17-ketosteroid assay with chorionic gonadotropin therapy. Albright and his co-workers believe that this syndrome is of pituitary origin. Chorionic gonadotropin produces no rise in the 17-ketosteroid excretion in male castrates and in eunuchoid patients with positive follicle-stimulating hormone tests.

Group 2, the pseudoendocrinopathies, is composed of those children who at some time during their growth period deviate from the normal but who do not have a real abnormality of any of the endocrine glands. A great number of prepubescents, who will ultimately develop into normal adults, are often mistakenly diagnosed as having endocrine disturbances. The problem in these cases relates to the size of the genitalia, obesity or growth. One of the commonest errors is concerned with the management of obese boys. The distribution of fat in these boys resembles that found in women and adult eunuchs. The physician is therefore inclined to make a diagnosis of obesity of the Fröhlich type, particularly since the genitalia appear small. This type of obesity is not at all abnormal in boys of a pyknic somatotype. The apparent hypogonadism is due to the fact that the penis is usually embedded in suprapubic fat. When the fat pad

FIGURE 4. *Pituitary Dwarfism in a Three-and-a-Half-Year-Old Boy.*

The height was only 75 cm., corresponding to that of a child of one year, as did the bone age.

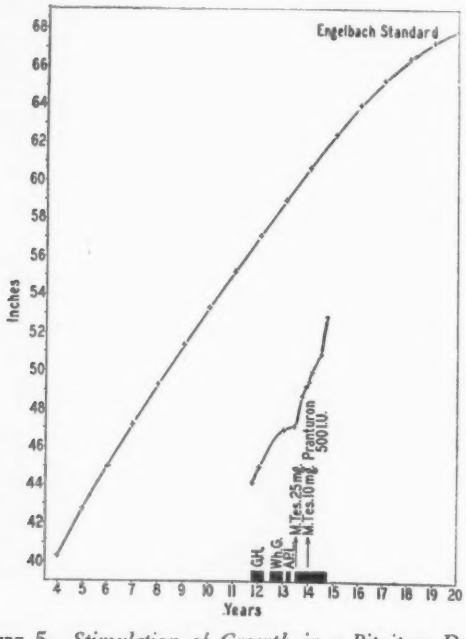


FIGURE 5. *Stimulation of Growth in a Pituitary Dwarf.*

The growth curve is compared with Engelbach's standard. The abbreviations are as follows: G.H., *growth hormone;* Wh.G., *whole gland;* A.P.L., *anterior-pituitary-like hormone; and* M.Tes., *methyltestosterone.*

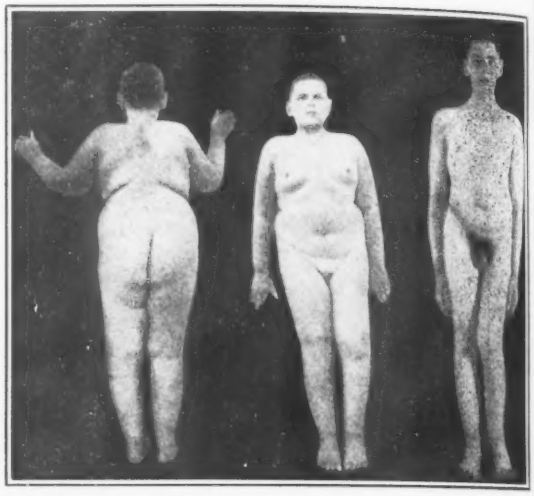


FIGURE 6. *Pseudo-Fröhlich Syndrome in a Fourteen-Year-Old Boy (Rosenstern[2]).*

The boy was of normal height but was markedly obese, with the testes embedded in suprapubic fat. The condition subsided spontaneously, and at eighteen years of age (photograph on right) the boy had normal build and complete sexual development.

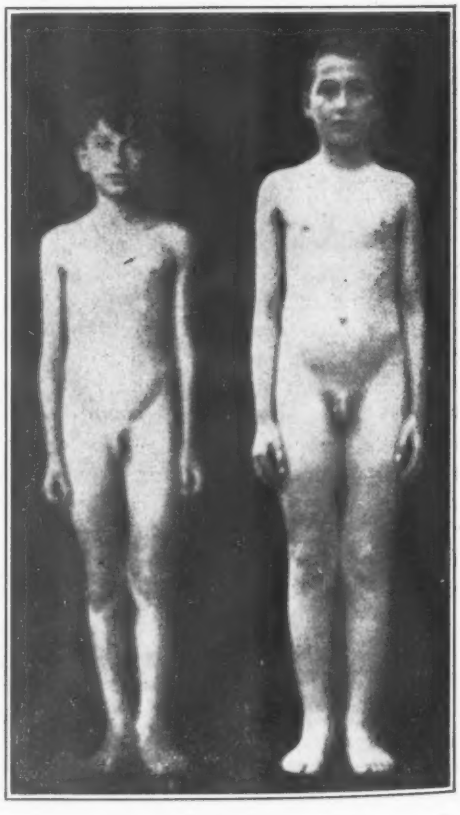


FIGURE 7. *Temporary Early Leanness (Rosenstern[2]).*

The photograph on the left shows leanness at eleven years of age; that on the right, an appreciable fat deposit with the advent of puberty at thirteen.

is pushed back and the penis and testes are measured, the genitalia are found to be within the normal range; furthermore, there is no delay in the onset of pubescence and development may occur earlier than usual. Since there is no hypogonadism, the diagnosis of adiposogenital dystrophy of Fröhlich's type is not at all justifiable. After reaching the age of maturity, most of these boys grow taller and slimmer, although they maintain their characteristic somatotype through life. Treatment consists of a low-calorie diet, particularly low in carbohydrates and fat, supported by thyroid medication (Schonfeld[11]). At the beginning it is advisable to adjust the intake below the basal metabolism and induce the patient to burn his own body fat.

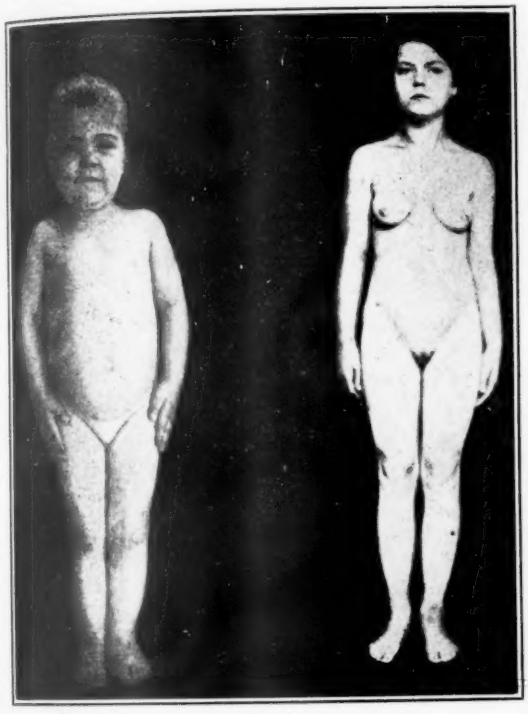


FIGURE 8. *Temporary Early Obesity (Rosenstern[2]).*

The photograph on the left shows obesity at five and a half years of age; that on the right, the normal build acquired spontaneously at thirteen.

Figure 6 shows a case of pseudo-Fröhlich syndrome. At fourteen years the patient had all the characteristics of obesity of prepubescence. Four years later all signs had subsided. He is now completely mature. No specific treatment was supplied. The pseudo-Fröhlich syndrome occurs in girls as well as in boys. There are other pseudoendocrine problems in girls, some of which are concerned with anomalies of the menstrual period.

That in many of these cases of obesity one is dealing simply with an accentuation of a physio-

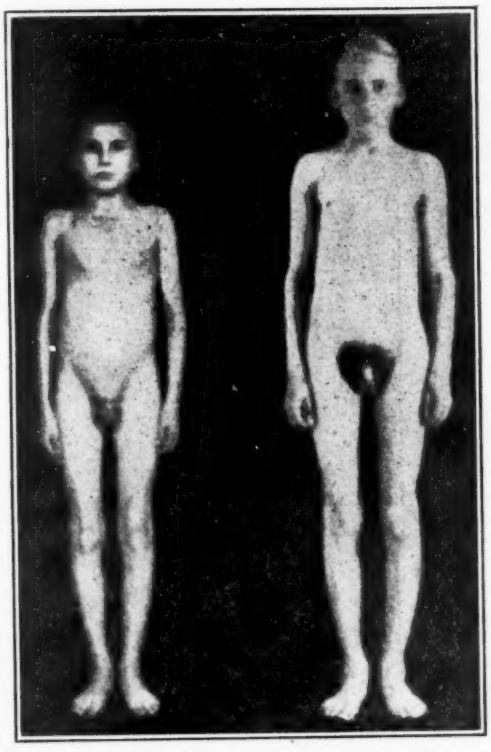


FIGURE 9. *Late Sexual Development in Universal Infantilism (Rosenstern[2]).*

The photograph on the left shows that sexual development had not begun at the age of seventeen; that on the right, that it had been completed at twenty-two. The patient suffered from chronic asthma.

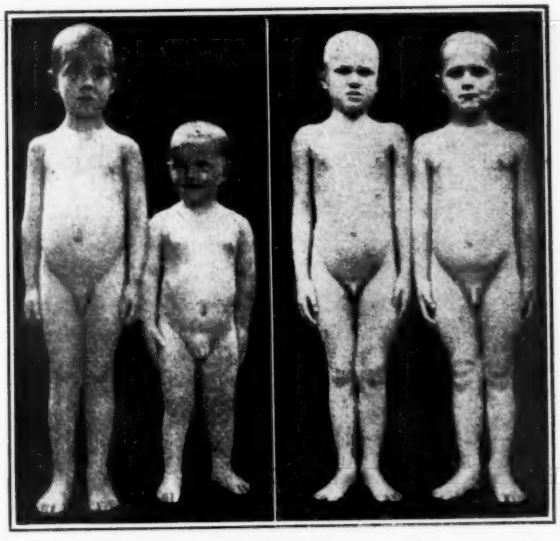


FIGURE 10. *Temporary Stunting of Stature (Rosenstern[2]).*

In the photograph on the left, the boy on the right is much shorter than the normal boy of five and a half years on the left; in that on the right, the same boy (at the right) is equal in height to a normal boy of seven and a half years (at the left).

logic phase is shown in Figure 7. Prepuberty in itself is physiologically associated with a heavier fat deposit. This patient was fairly slender at eleven years. Two years later he had a good fat deposit with beginning puberty. If such a fat deposit is overaccentuated, an obesity may easily result that imitates the Fröhlich picture. Familial factors and also certain habits may help to bring about the condition. Of particular importance is excessive food intake, since the appetite is always increased during pubescence. The basal metabolic rate in this phase is higher, the specific dynamic action of food is low, and children may gain weight excessively. Transitory obesity may also occur at an earlier period of childhood, as illustrated in Figure 8. No endocrine background was detectable in this patient.

In certain cases retarded sexual development can also be included under the heading of pseudoendocrine problems. Figure 9 shows a boy with transitory universal infantilism. The left side of the picture shows the patient at the age of seventeen years; he is completely undeveloped. On the right side he is shown five years later as a perfectly matured young man. No stimulating treatment was applied. He made up his retardation spontaneously. Familial tendencies are usually contributory in these cases.

Group 2 offers many other situations, such as stunting of the stature in certain periods of childhood. This is a complex phenomenon, and each case must be studied carefully. On the whole, one can say that the chances of making up the difference in height are better the younger the child and the less differentiated his skeleton. If the x-ray age is definitely below the chronologic age, the prognosis is usually good. Figure 10 shows that watchful waiting is sometimes the best treatment.

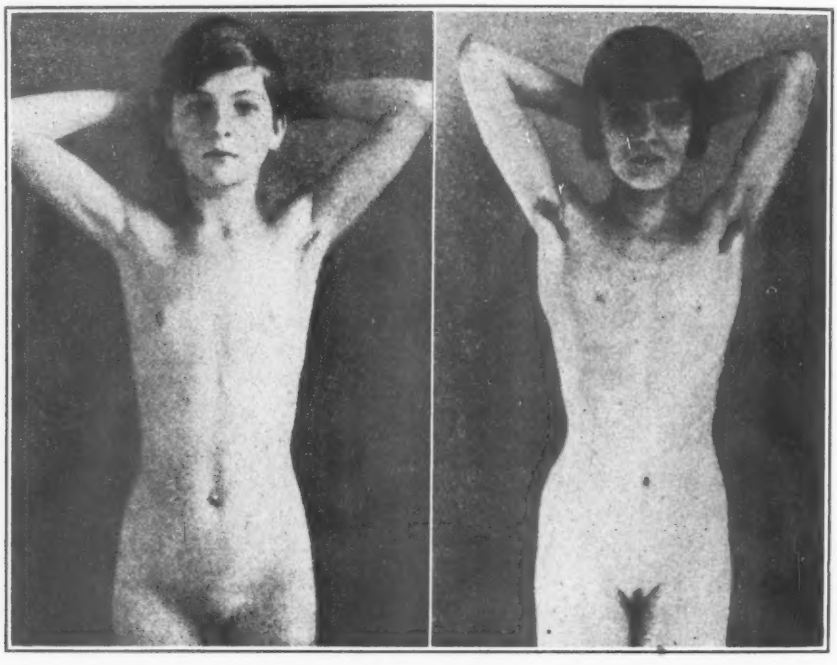


FIGURE 11. *Disharmonic Sexual Development (Priesel and Wagner[2]).*

Both girls were about twelve years old. Axillary hair was the only extragenital characteristic, there being no pubic hair or breast development.

Another problem that should be briefly mentioned is what may be called disharmonic sexual development. Figure 11 shows two girls, one of twelve years and 5 months and the other of eleven years and six months, who showed axillary hair as the first sign of pubertal development. This usually develops as the last extragenital characteristic, often only after the menarche. No pubic hair and no breast development were present in these cases. What this phenomenon means is difficult to say, and very little is known about it. No endocrine studies were carried out in these cases, particularly so far as the study of the sex hormones was concerned.

Disharmonic development is sometimes detectable only by x-ray. Recently a child of about four was observed who was treated as a case of hypothyroidism for a considerable length of time because of somewhat retarded development. This patient was below the expected height for her age. The development of the ossification centers was delayed, being that of about eighteen months of

age. Otherwise she revealed only a few stigmas: broadening of the bridge of the nose, prominent epicanthus and strabismus. On thyroid treatment she developed, but not so strikingly as was expected in true hypothyroidism. Thyroid treatment was discontinued for six months. At the end of this period she showed good progress of growth in height as well as in differentiation, but the order of appearance of the newly forming ossification centers was not consistent with the regular order. The major multangulum became visible in one wrist but was missing in the other. The lunatum was not yet detectable. This development can be classified as almost precipitated, since the ossification of the major multangulum belongs to a later period of development. A similar behavior of the ossification centers is known in mongolian idiocy. This case properly belongs in Group 3, the large group of congenital anomalies with endocrine features.

* * *

These few problems demonstrate how complex are the endocrine problems in childhood. One should beware of becoming a victim of self-deception as a result of applying treatments that are not exact scientific achievements. The significance of many laboratory tests, such as the glucose-tolerance test and determination of the basal metabolic rate, is often overemphasized. Clinical evaluation, including body measurements, is still the most important part of the study in any given case. The fact that the term "endocrine imbalance" is used loosely and frequently is an indication that the problem is not clearly understood.

370 Commonwealth Avenue

References

1. Nobel, E., Kornfeld, W., Ronald, A., and Wagner, R. *Innere Sekretion und Konstitution im Kindesalter*. 352 pp. Vienna: Wilhelm Maudrich, 1937.
2. Rosenstern, I. Über temporäre Disharmonien der körperlichen Entwicklung im Kindesalter. *Kinderärztl. Praxis* 4:18-31, 1933.
3. Priesel, R., and Wagner, R. Gesetzmässigkeiten im Auftreten der extragenitalen sekundären Geschlechtsmerkmale bei Mädchen. *Ztschr. f. Konstitutionslehre* 15:333-352, 1930.
4. Moricard, R., and Bize, P. R. Développement du pénis provoqué chez l'enfant par l'injection d'acétate de testostérone. *Compt. rend. Acad. d. sc.* 204:1044, 1937.
5. Villaret, M., Justin-Besançon, L., and Rubens-Duval, A. Remarques sur les effets du propionate de testostérone dans un cas d'eunuchisme post-pubère. *Compt. rend. Soc. de Biol.* 127:599-601, 1938.
6. Webster, B. Treatment of hypogonadism in adolescent male. *J. Pediat.* 13:847-858, 1938.
7. Webster, B., and Hoskins, W. Influence of androgen therapy on growth rate of hypogonadal adolescent boys. *Proc. Soc. Exper. Biol. & Med.* 45:72-75, 1940.
8. Browne, J. S. L., and Ross, A. Personal communication.
9. Miescher, K., and Tschopp, E. Ueber orale Wirksamkeit männlicher Sexualhormone. *Schweiz. med. Wchnschr.* 19:1258, 1938.
10. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C. Colorimetric assay of 17-ketosteroids in urine: survey of use of this test in endocrine investigation, diagnosis, and therapy. *J. Clin. Endocrinol.* 1:234-256, 1941.
11. Schonfeld, W. A. Management of male pubescence. *J. A. M. A.* 121:177-182, 1943.

FUNCTIONAL URINARY INCONTINENCE IN WOMEN*

A Report of Twenty-Three Cases Treated by the Kennedy Operation

LOUIS E. PHANEUF, M.D.,† ROY J. HEFFERNAN, M.D.,‡ AND S. CHARLES KASDON, M.D.§

BOSTON

POOR bladder control is one of the most distressing conditions that the gynecologist is called on to correct. The woman with complete or partial urinary incontinence suffers not only the physical discomfort attending the leakage; her social life, if it exists at all, is one of constant fearful apprehension.

Lack of proper control may be caused in various ways. The defect may be congenital, such as hypospadias or epispadias. Some form of urinary fistula may result from a gynecologic operation or a difficult accouchement. The latter, a common condition in the early days of obstetrics, is now rarely seen. Neoplasms of the bladder or other pelvic tumors may make the sphincter mechanism incompetent, or the etiology may be neurologic, as in disease of the spinal cord. The type most frequently seen, however, is known as stress or functional incontinence, in which the sphincteric action of the bladder neck and urethra has been impaired by childbirth. The purpose of this article is to evaluate an operative procedure for the relief of stress incontinence and to report the results obtained in 23 cases treated by this method.

The anatomy and physiology of the urethra and bladder have received widespread study, but only in the last ten years has it been possible to correlate in a comprehensible way the many structures present. Martius[1] has advanced this knowledge greatly and has described several operative procedures for the treatment of urinary incontinence, including fascial transplants from the abdomen and ischiocavernosus transplants as well as plication technics. Goebell[2] used the pyramidalis muscles to support the weakened urethra and bladder neck.

Lately Aldridge[3] has devised a new method for a similar procedure. These operations are valuable

*Presented at the annual meeting of the New England Obstetrical and Gynecological Society, December 2, 1942.

From the Department of Gynecology, Tufts College Medical School, and the Obstetrical and Gynecological Department, Carney Hospital, Boston.

†Professor and head of Department of Gynecology, Tufts College Medical School; obstetrician-in-chief and gynecologist-in-chief, Carney Hospital.

‡Instructor in gynecology, Tufts College Medical School; obstetrician and gynecologist, Carney Hospital.

§Assistant obstetrician and gynecologist to outpatients, Carney Hospital.

adjuncts to the plication technics in increasing the number of favorable results. The best promise of satisfactory treatment, however, has issued from the recent work of Kennedy.

Most plastic operations involving the vesical neck and urethra are based on the original Kelly[4] principle, which outlines the mattress suturing of the bladder neck and urethral sphincter. Briefly, the operation consists of exposing and separating the urethra and bladder through a longitudinal incision in the anterior vaginal wall and the approximation of the torn or relaxed sphincter muscles and fascia.

Kennedy[5] describes the most frequent causes of incontinence as follows: trauma to the inner and middle third sphincters of the urethra, causing them to become partially fixed by fine bands to the posterior lateral margins of the adjacent pubic rami; and damage in the midline to those voluntary fibers that pass under the middle third of the urethra and are attached to each ramus of the pubis, posteriorly constituting a sling support.

Subsequent to a careful study of the anatomy and physiology of the bladder and urethra, and after the use of roentgenography in elaborating the function of the urethra, Kennedy reported that it was possible to cure incontinence by breaking down the fine bands between the urethra and the pubic rami and plicating the urethra in its midline to prevent any further connection with the rami laterally, and bringing together in the midline beneath the inner and middle thirds of the urethra the injured "sling" fibers. He[6] reasoned that the voluntary sphincters functioned better when they were circular and without attachments and were suspended freely in a sling. He presented a detailed exposition of the technic employed to obtain these conditions.

The reports of the results in operative procedures for urinary incontinence vary according to the methods used and the ability of the plastic surgeon, as well as the period of time that elapses between the injury and its repair. It is obvious that the fascia and muscle fibers to which Kennedy attaches so much importance are available for only a limited time. Their attenuation after years of relaxation and injury makes their approximation problematical and the end results irregular. Since many of the women who seek treatment have endured incontinence for years, the reports of satisfactory repair show remarkable variation. One of the early papers concerning the surgical treatment of urinary incontinence is that of Kelly and Dumm,[7] who had successful results in 75 per cent of 20 treated cases. Watson[8] operated on 105 cases, with success in 66 per cent, improvement in 22 per cent and no improvement in 12 per cent. He also found that two out of three patients with incontinence showed a cystocele.

Furniss[9, 10] reported 17 cases of incontinence treated surgically. Success was obtained in 76 per cent and relief of symptoms in 11 per cent, and there was operative failure in 13 per cent. Of 28 consecutive operations by Kennedy,[6] only 2 were failures; that is, 93 per cent were completely satisfactory. Peightal,[11] in a discussion of Kennedy's work, revealed that 11 of 12 cases were successfully treated by the latter's technic. Stress incontinence was present in the single failure. According to Barnes,[12] the cures vary from 36 to 100 per cent and repeat surgery from 6 to 15 per cent. He emphasized the general inadequacy of the treatment. Matassarin[13] revealed that 10 to 20 per cent of the patients visiting Schaumann's gynecologic clinic have urinary dribbling and 1 to 2 per cent have complete loss of control. He believed that 90 per cent of these patients would secure continence from simple cystocele repair and that the remaining 10 per cent would respond only to a more extensive operative procedure. In his hands, plication of the urethra in the anteroposterior plane with the addition of Kelly stitches placed at the trigone resulted in a complete cure in 6 cases. Berkow[14] stated that when the Kelly technic is employed, 15 to 40 per cent failures are revealed by the literature. His own procedure differs from that of Kennedy in that he does not free the fascial sling so widely, but rather raises the urethra to the clitoris and closes the structures beneath it. He analyzed 19 cases from two months to three years after operation and found that 89 per cent were continent. Aldridge[3] believes that 10 to 20 per cent of the operations for urinary incontinence fail.

Technic of Kennedy Operation

In the Kennedy operation for incontinence, the cervix is fixed by a Jacob's volsellum, if it comes down readily; if not, the anterior vaginal wall is picked up at the level of the uterine isthmus by a guy suture of black silk. A second guy suture of the same material is placed in the anterior vaginal wall 1 cm. below the urinary meatus. A longitudinal incision is made in the anterior vaginal wall between these two sutures. It starts about 1.5 cm. below the urinary meatus and ends about 1.5 cm. above the suture placed at the level of the uterine isthmus. The anterior vaginal wall is dissected from the urethra and the bladder (Fig. 1). The urethra is next separated from the pubic ramus on each side. By starting the separation close to the bone, a plexus of veins and branches of the inferior vesical artery may be avoided. If these vessels are torn, they are picked up and ligated with fine chromic catgut.

The separation is carried out into the paravesical space. This dissection is facilitated by retracting the edges of the vaginal wall by means of guy sutures of black silk or by Allis forceps. The

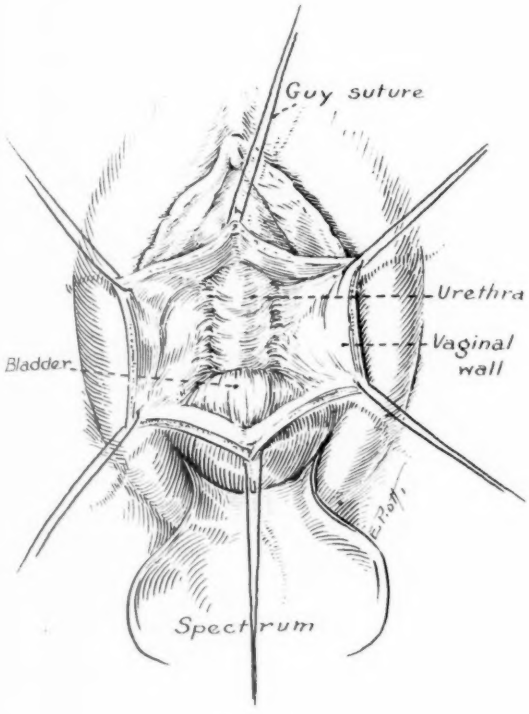


FIGURE 1.

The anterior vaginal wall has been opened to within 1.5 cm. of the external urinary meatus. The urethra has been separated from pubic rami, and the bladder neck is exposed.

fibrous adhesions between the urethra and the pubic rami having been severed, the former regains its mobility. In order to restore and maintain continence, the urethra must not be permitted again to become adherent to the pubic rami. With this end in view, the tissues under the urethra are plicated by three mattress sutures of No. 1 chromic catgut, which, when tied, keep the urethra away from the pubic rami (Fig. 2). A second row of three mattress sutures introduced in the edges of the fascia-like structures on each side of the urethra further separates it from the pubic rami (Fig. 3). If necessary, a fourth mattress suture may be placed at the lower part of the urethra in the region of the internal sphincter (a suture placed in this region formed the basis of the Kelly operation for incontinence). The excess of the anterior vaginal wall on each side that formed the urethrocele is then resected. In accomplishing this, the damaged portion of the voluntary sphincter is removed with the vaginal wall.

The intact voluntary sphincter fibers that remain after the resection of the vaginal wall are approximated by No. 1 chromic catgut sutures, usually three in number, with simultaneous closure of this portion of the anterior vaginal wall. These chromic catgut sutures begin at the highest point of the vestibule and extend down about 2 cm. In their course, they pick up the vaginal wall close to the pubic rami, so as to enclose the muscle fibers of the constrictor urethrae muscle (voluntary) and the inferior layer of fascia of the uro-

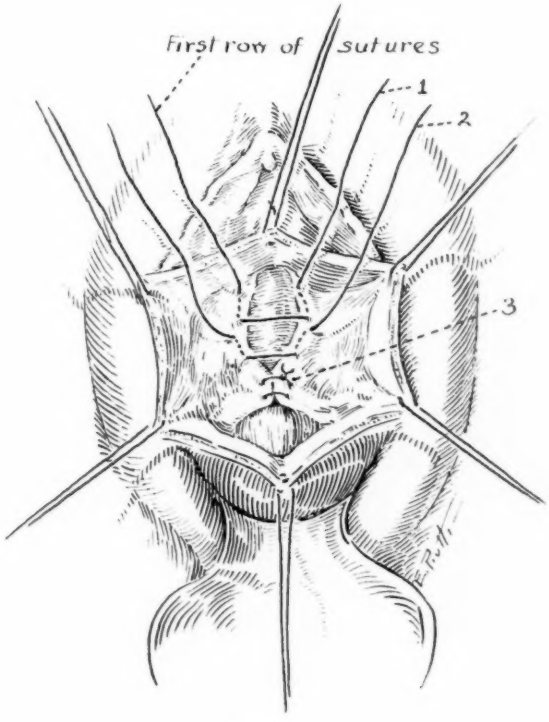


FIGURE 2.

Three mattress sutures of No. 1 chromic catgut have been placed in the fascia-like structures on the sides of the urethra. When tied, they pull the urethra away from the pubic ramus of each side. The lower mattress suture (3) plicates the vesical sphincter.

genital diaphragm on both sides. The remainder of the anterior vaginal wall is closed with similar sutures (Fig. 4). Originally, we used silver wire for the three uppermost sutures in the anterior vaginal wall, as recommended by Kennedy, but this has been replaced by No. 1 chromic catgut sutures without any apparent change in the result. A plain, male soft-rubber catheter is introduced into the urethra and left in as an indwelling catheter for seven days. The patient usually voids normally after its removal, and she is allowed out

of bed on the tenth postoperative day. Figure 5 illustrates the completed operation.

Results

A detailed survey of 23 cases, all of which received typical Kennedy operations, revealed the following data. The average age of patients was 47.1 years, the youngest being thirty-five and the oldest sixty-nine. In the thirty-to-thirty-nine-year group there were 4 cases, in the forty-to-forty-nine year group 13 cases, in the fifty-to-fifty-nine-year group 2 cases, and in the sixty-to-sixty-nine-year group 4 cases. The average parity was 3.6. Primigravidas numbered 3 (13 per cent), biparas 3, triparas 5 (22 per cent), quartiparas 5, quinparas 4 (17 per cent), sexiparas 2 (9 per cent) and septiparas 1 (4 per cent). Seven (30 per cent) of the patients had undergone previous operations for their urinary incontinence; in 5 of these cases (22 per cent) the procedures were cystocele repairs.

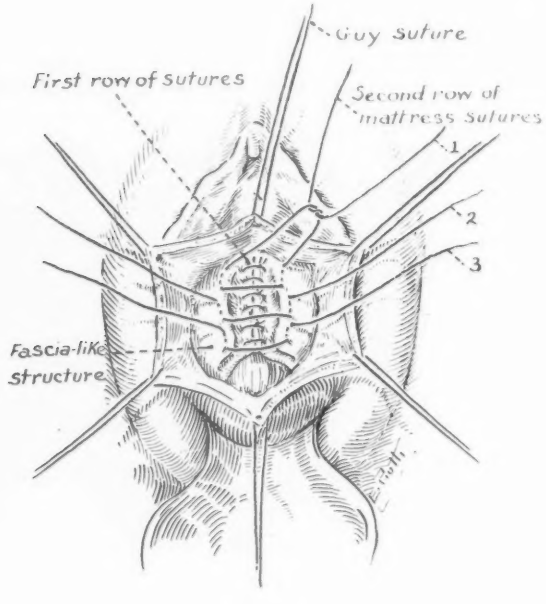


Figure 3.

A second row of three mattress sutures of No. 1 chromic catgut has been placed in the fascia-like structures on the sides to enfold further the urethra and pull it away from the pubic rami.

The presenting symptom of incontinence had existed for widely divergent lengths of time, with an average period of ten years and three months. The shortest duration was seven months and the longest thirty-two years. Three patients (13 per cent) had had incontinence for less than one year, 4 (17 per cent) for one to four years, 6 (26 per cent) for five to nine years, 6 for ten to nineteen years, 1 (4 per cent) for twenty to twenty-nine years, and 1 for more than thirty years. Two patients had slight stress incontinence of indeterminate duration.

In addition to the primary urethral relaxation, there were 13 cases (57 per cent) of concomitant cystocele, 10 cases (44 per cent) of relaxed vesical sphincter, some with previous cystocele repair, and but 3 cases (13 per cent) of relaxed urethral sphincters alone. Seventeen of the patients also received gynecologic surgery in addition to the Kennedy operation; namely, trachelorrhaphy in 1 case, the Manchester operation in 3 cases, posterior colporrhaphy in 2 cases, perineorrhaphy in 12 cases, hysterectomy in 2 cases, and cervical amputation in 5 cases. Only two anesthetics were used — spinal in 14 cases (61 per cent) and general in 9 cases (39 per cent). The average length of hospitalization was 17.1 days, with the majority of patients (18 cases) remaining for thirteen to sixteen days. Except for mild transient cystitis (5 cases) that responded immediately to conservative therapy, there were no postoperative complications.

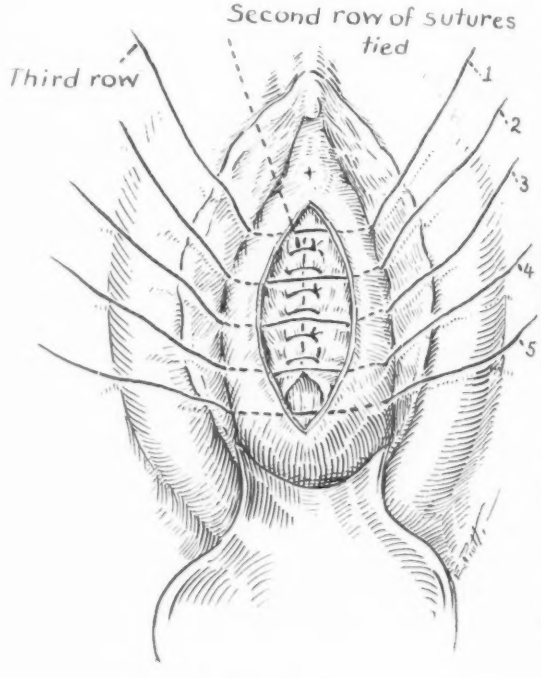


Figure 4.

The constrictor urethral muscle and the urogenital diaphragm have been reconstructed, and the remainder of the incision in the anterior vaginal wall is about to be closed.

All the patients were successful in controlling their urine two to four weeks postoperatively. One woman who had a dilatation and curettage.

cervical amputation, Kennedy operation and perineorrhaphy experienced some hesitancy at the beginning of micturition, but this gradually disappeared. The late results were likewise gratifying. Late check-ups on all the patients included in this report were obtained from two months to four years and nine months after operation, with an average period of seventeen months. Complete late recovery of bladder function was attained in 18 cases (78 per cent), and marked improvement in 3 cases (13 per cent). The total number of cases with either complete recovery or marked improvement was therefore 21 (91 per cent). The failures numbered 2 (9 per cent); a study of these follows. In no case was there any aggravation of symptoms after surgery.

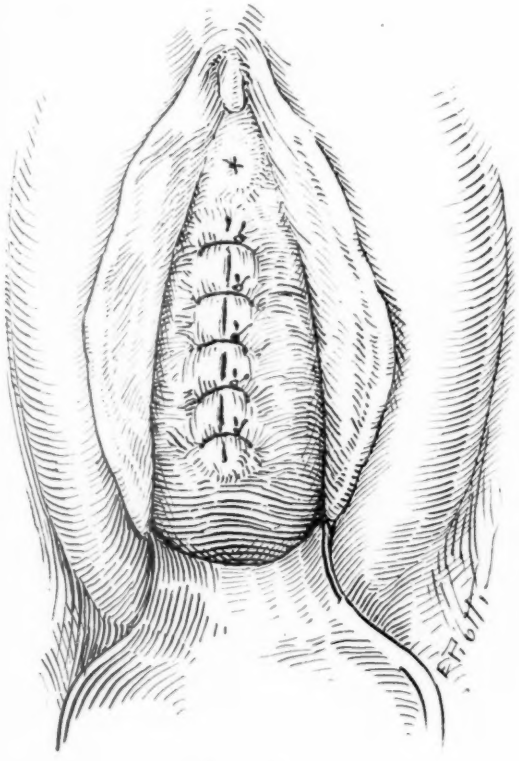


FIGURE 5.

This sketch shows the result of the completion of the operation.

CASE REPORTS

CASE 1. Mrs. M. H., a 46-year-old quartipara, had had dribbling and stress incontinence for 17 years. A relaxed vesical sphincter and moderate cystocele were present. No previous surgery had been attempted. A dilatation and curettage, Kennedy operation and perineorrhaphy were done under spinal anesthesia, and the postoperative convalescence was uneventful. When a discharge examination was made 15 days after surgery, the urinary control was excellent, but within 2½ years the stress incontinence had returned to its original degree. In retrospect, this case might have responded better to such a procedure as that of Aldridge,[3] in which abdominal fascia is used as a sling for the weakened urethral sphincter.

CASE 2. Mrs. H. C., a 41-year-old tripara, had had incontinence for 7 years associated with a relaxed sphincter. Throughout her 14 days in the hospital, the bladder function was perfect, but 3 months later the incontinence was as severe as on entry.

DISCUSSION

The need of a careful urologic study in incontinent women is self evident. Barnes[12] has suggested three tests for adequate diagnosis and evaluation of the type of incontinence, giving the technic of each: direct measurement of intravesical pressure, direct measurement of urethral resistance and indirect measurement of internal sphincter strength. His work emphasizes the fact that stress incontinence is the result of failure of the voluntary urethral sphincter fibers to function. The involuntary fibers control other vesical pressures. This suggests that operations such as that of Aldridge[3] are of great benefit in cases where stress incontinence is superimposed on general urinary dribbling. The inadequacy of the Kennedy procedure alone in such cases is well illustrated in the first of our two failures.

It is important to re-emphasize the significance of the lapse of time between the injury that caused the incontinence and the treatment of the condition. In our first failure seventeen years had elapsed, and in the second seven years. It is possible that an incontinent patient with a cystocele and urethral sphincter relaxation of more than five years' duration requires more than an anterior colporrhaphy. In especially recalcitrant problems resort to the methods of Goebell[2] and Aldridge[3] is of real value.

SUMMARY

A presentation of the general problems of urinary incontinence in women is made.

Twenty-three women with incontinence were treated by the Kennedy operation, with either marked improvement or complete late recovery of bladder function in 91 per cent in an average of seventeen months after operation.

Two failures occurred in the series; the possible causes for failure are discussed.

Suggestions are offered regarding the study, classification and treatment of urinary incontinence in women.

REFERENCES

1. Martius, H. Uber Harnfistel- und Inkontinenzoperationen. *Zentralbl. f. Gynäk.* 60:194-204. 1936.

2. Goebell, R. Zur operativen Beseitigung der angeborenen Incontinentia vesicae. *Ztschr. f. gynäk. Urol.* 2:187-191, 1910.
3. Aldridge, A. H. Transplantation of fascia for relief of urinary stress incontinence. *Am. J. Obst. & Gynec.* 44:398-411, 1942.
4. Kelly, H. A. *Gynecology.* 1043 pp. New York and London: D. Appleton and Company, 1928. Pp. 821-823.
5. Kennedy, W. T. Incontinence of urine in female: some functional observations of urethra illustrated by roentgenograms. *Am. J. Obst. & Gynec.* 33:19-29, 1937.
6. *Idem.* Incontinence of urine in female, urethral sphincter mechanism, damage of function, and restoration of control. *Am. J. Obst. & Gynec.* 34:576-589, 1937.
7. Kelly, H. A., and Dumm, W. M. Urinary incontinence in women without manifest injury to bladder. *Surg., Gynec. & Obst.* 18:444-450, 1914.
8. Watson, B. P. Imperfect urinary control following childbirth and its surgical treatment. *Brit. M. J.* 2:566-568, 1924.
9. Furniss, H. D. Incontinence of urine due to relaxed vesical sphincter. *Am. J. Obst. & Gynec.* 8:195-198, 1924.
10. *Idem.* Suprapubic sphincter tightening. *Am. J. Obst. & Gynec.* 9:503-506, 1925.
11. Peightal, T. C. Discussion of Kennedy.[6]
12. Barnes, A. C. Method for evaluating stress of urinary incontinence. *Am. J. Obst. & Gynec.* 40:381-390, 1940.
13. Matassarin, F. W. Rose operation repair of trigonal muscle (incontinence in female). *J. Kansas M. Soc.* 41:189-192, 1940.
14. Berkow, S. G. Paraurethral fixation: new operation for cure of relative incontinence of urine in women. *Am. J. Obst. & Gynec.* 41:1051-1056, 1941.

CLINICAL NOTE

ACTINOMYCOSIS OF THE CHEST WITH SPREAD TO THE ABDOMEN*

Report of a Case Cured with Sulfadiazine

William E. Ladd, M.D.,† and Alexander H. Bill, Jr., M.D.‡

BOSTON

BECAUSE of the known severity of actinomycosis, particularly with thoracic involvement, we have thought it worth while to present the following case. The older literature shows a poor prognosis for actinomycosis of the chest. Of the cases reviewed at the Royal Victoria Hospital by Morton,[1] 5 out of 7 thoracic cases resulted in death. This was in contrast to the somewhat better prognosis for the abdominal cases and the considerably better prognosis for the cervicofacial group. This impression is confirmed by Cope,[2] Hanes[3] and Schmitt and Olsen.[4]

In the last five years a number of reports of successful treatment of actinomycosis with sulfonamides have appeared. The first is that of Walker,[5] who treated a soldier with appendiceal actinomycosis and a draining sinus. Sulfanilamide was used, with dramatic results. Following this case, the reports of Hall,[6] Sudler and Johnson[7] and Miller and Fell[8] in this country and of Dorling and Eckhoff[9] and Ogilvie[10] in England appeared in fairly quick succession. Others[11-14] followed. The cases reported were all treated with sulfanilamide or sulfapyridine, with cure or improvement. In some cases other means of treatment, such as x-ray and iodides, were used together with the sulfonamide drug. The use of sulfathiazole is reported in only 1 case, in which it was unsuccessful after a very short course of therapy.[15] Two of the cases reported above were of the thoracic type (Wilkinson[11] and Dobson et al.[13]). None of these reports contain cases treated with sulfadiazine.

The rationale of the sulfonamide treatment of actinomycosis has been studied by Cutting and Gebhardt,[16] who have shown that the growth of *Actinomyces hominis* in vitro is inhibited by the drugs. Of the drugs studied by these authors, sulfathiazole and sulfadiazine were found to be about equally effective and to be more effective than sulfanilamide in similar concentration. On the strength of this study and because of the low toxicity of sulfadiazine, it was used in the treatment of our case.

Case Report

D. O'K., a 9-year-old boy, was admitted to the Surgical Service of the Children's Hospital on January 31, 1942, complaining of draining sinuses of the back and right flank.

Sixteen months before admission the patient had developed a cough and fever. This continued until 14 months before admission, when an egg-shaped swelling appeared on the right chest posteriorly. The patient's physician sent him to a hospital near his home, where it was thought that he had empyema necessitatis. An x-ray film of the chest showed slight density at the right base, which was interpreted as probably in the lung rather than in the pleura. This swelling was drained and proved to be an abscess. Surgical and medical measures were undertaken, and during the next 12 months the patient underwent six operations for drainage of persistent and spreading abscesses on the posterior chest and in the right flank. The right pleural and subdiaphragmatic spaces were opened for drainage during this time. He is reported to have been given sulfapyridine and sulfanilamide at times, but the quantity given and the duration of treatment were unknown. Clinically he did poorly, with profuse drainage and gradual loss of strength. Two months before admission he was taken home from the local hospital against the advice of his physician.

During his stay at home the patient continued to go downhill. He was feverish in the evening and coughed continuously. On two occasions he coughed up blood. Also, he developed pain on straightening his right leg. His condition grew progressively worse, and he was admitted as an emergency case 16 months after his first symptoms.

The patient lived in the factory district of a small New England shoe town. His mother and father and one brother were healthy. The past history was negative.

Physical examination showed a feverish, emaciated and apprehensive boy weighing only 49 pounds. He was

*From the Surgical Service of the Children's Hospital and the Department of Surgery, Harvard Medical School.

†William E. Ladd Professor of Child Surgery, Harvard Medical School; Chief of Surgical Service, Children's Hospital.

‡Formerly, intern, Children's Hospital.

occasionally seized with paroxysms of coughing. The skin was loose, pale and dry, and was covered with fine lanugo-like hair. The back was honeycombed with sinuses interspersed with raw areas of granulation. Thick, yellow pus could be expressed from the sinuses. One sinus extended into the right flank, apparently beneath the liver, for the length of a Kelly clamp. There were doubtful on admission, positive on February 6, and negative on February 12. A Congo red test showed no retention of dye. Examination of the pus revealed no sulfur granules or fungus. Stains and guinea-pig inoculations showed no tubercle bacilli.

X-ray examination of the chest on admission showed cardiac enlargement, bilateral pleural effusion and increase

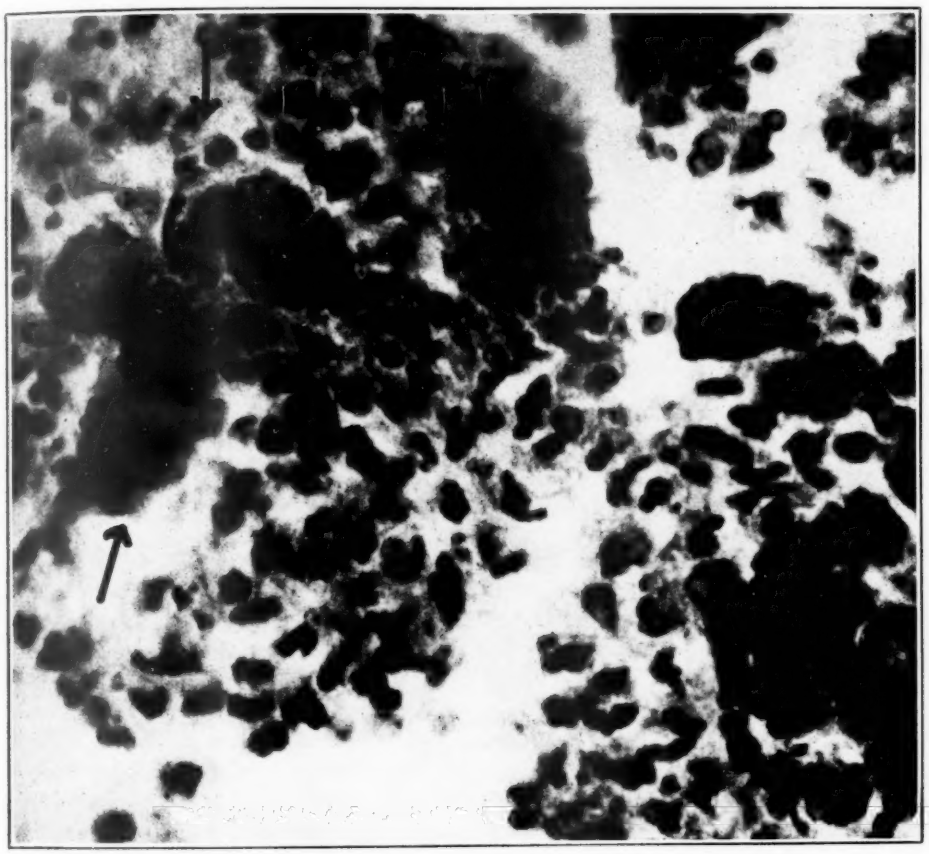


FIGURE 1. *Photomicrograph of Granulation Tissue Showing a Cluster of Actinomyces (× 700).*

rales in the right chest and dullness anteriorly up to the 4th rib. The left side of the chest was clear. There was an apical systolic murmur (Grade III), with a precordial thrill. The abdomen was distended and shiny, and there was an area of flaccidity and sensory loss below an operative scar in the right upper quadrant. The operative scar extended into an abscess involving the abdomen below the liver. The presence of free fluid in the abdomen was suspected but was never proved. The spleen was palpated 4 fingerbreadths below the ribs on the right. The right hip was held in 45° of flexion and could not be straightened. There was suggestive clubbing of the fingers and toes.

Laboratory examination showed a red-cell count of 3,400,000 and a white-cell count of 33,600, with 74 per cent neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. Examination of the urine was normal on admission and remained so throughout the hospital course. Two blood cultures taken shortly after admission were negative. The blood nonprotein nitrogen was 25 mg. per 100 cc. and the serum protein was 7.4 mg. Blood Hinton reactions were in the lung markings in the lower two thirds of each lung field. Portions of the 10th and 11th ribs had been resected on the right.

The patient was studied for the first 5 days, during which time he required several copious dressings to the back each day. The temperature reached 102 or 103°F. each evening, and he was frequently shaken with a severe nonproductive cough.

On the 6th day, incision and drainage of the deepest sinus in the right flank were carried out. A biopsy of this tissue was taken, and pathological examination of the granulation tissue showed "peculiar yellowish-brown staining masses with club ends around the periphery, characteristic of actinomycosis."

The patient continued to run a fever and on the 12th day was started on sulfadiazine, 0.5 mg. six times a day. The temperature fell to normal after 5 days of this therapy and remained normal subsequently. The drainage became negligible within 2 weeks. The right leg was put in traction and physiotherapy was given, with gradual return of motion. The sulfadiazine level was followed every 3 or 4 days and remained chiefly between 8 and 12

mg. per 100 cc., the lowest level recorded being 4.5 mg. and the highest 14.5 mg.

The drug was continued, and after 4 weeks the patient had gained 5 pounds and seemed much better. After 6 weeks the back was dry and epithelialized. The sulfadiazine dose was cut to 0.5 mg. four times a day, but the level remained within the former range. After 8 weeks the patient was walking, and subsequent to this his convalescence was uneventful. He was discharged on May 20, weighing 63 pounds.

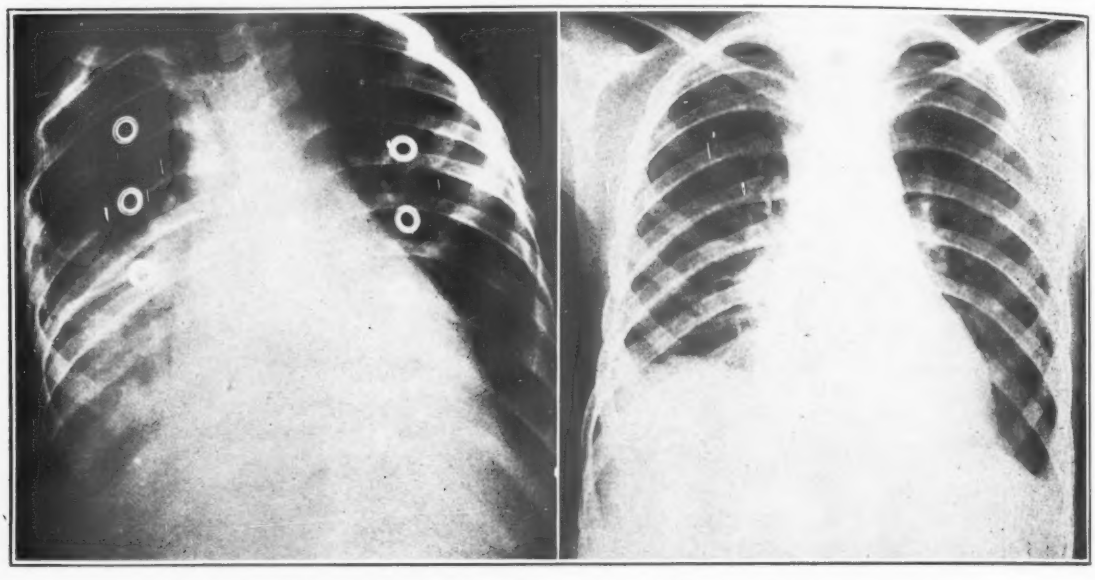


FIGURE 2. *Photographs of X-Ray Films of the Chest before and after Treatment.*

The film on the left shows actinomycotic involvement of the right lung; that on the right, taken five months later, shows complete clearing.

For 8 months after discharge sulfadiazine was continued at a dosage of 1.5 mg. daily, and the patient was seen at regular intervals.

On June 16, 5 months after admission and about 1 month after discharge, there were no signs in the chest.

On his latest visit, on February 15, 1943, the patient was not recognizable as the same boy who had been admitted a year previously. He weighed 85 pounds and walked without a limp. The cardiac murmur had disappeared, the chest was clear, and the sinus tracts were well healed. The spleen was no longer palpable, and the liver could just be felt. The weakness of the abdominal wall on the right was still present. X-ray films showed the right diaphragm to be still somewhat raised, but the lungs were normal. The patient was going to school and leading an entirely normal life.

SUMMARY

A review of the literature shows a group of cases of actinomycosis favorably influenced by treatment with sulfanilamide and sulfapyridine.

A case of actinomycosis in a nine-year-old boy is presented. The disease was of sixteen months' duration, starting in the chest and extending through the diaphragm into the retroperitoneal space. Treatment with sulfadiazine without other therapy resulted in a rapid cure.

300 Longwood Avenue

REFERENCES

1. Morton, H. S. Actinomycosis. *Canad. M. A. J.* 42:231-236, 1940.
2. Cope, Z. *Actinomycosis.* 248 pp. New York, London and Toronto Oxford University Press, 1938.
3. Hanes, F. M. Actinomycosis of lungs with thoracic fistulae: abscess of lower lumbar region: involvement of liver and spleen: poor therapeutic results with various treatments. *Internat. Clin.* 1:213-215, 1942.
4. Schmitt, G. F., and Olsen, A. M. Actinomycosis of thorax: report of two cases. *Proc. Staff Meet. Mayo Clin.* 16:506-509, 1941.
5. Walker, O. Sulfanilamide in treatment of actinomycosis. *Lancet* 1:1219, 1938.
6. Hall, W. E. B. Sulfanilamide in actinomycosis. *J. A. M. A* 112:2190. 1939.
7. Sudler, M. T., and Johnson, C. B. Treatment of actinomycosis with sulfanilamide: report of 2 cases. *J. Kansas M. Soc.* 40:330. 1939.
8. Miller, E. M., and Fell, E. H. Sulfanilamide therapy in actinomycosis *J. A. M. A.* 112:731, 1939.
9. Dorling, G. C., and Eckhoff, N. L. Chemotherapy of abdominal actinomycosis. *Lancet* 2:707-709, 1940.
10. Ogilvie, W. H. Abdominal actinomycosis cured with sulfapyridine. *Brit. M. J.* 2:254, 1940.
11. Wilkinson, E. E. Actinomycosis treated with sulfanilamide. *J. Pediat.* 18:805-810, 1941.
12. MacCharles, M. R., and Kippen, J. W. Three cases of actinomycosis treated with sulfanilamide. *Canad. M. A. J.* 41:490, 1939.
13. Dobson, L., Holman, E., and Cutting, W. C. Sulfanilamide in therapy of actinomycosis. *J. A. M. A.* 116:272-275, 1941.
14. Mitchell, H. S. Sulfapyridine in actinomycosis. *Canad. M. A. J.* 46:584, 1942.
15. Woodman, T. W. Abdominal actinomycosis: case report. *Southwest Med.* 25:81-83, 1941.
16. Cutting, W. C., and Gebhardt, L. P. Inhibitory effects of sulfonamides on cultures of *Actinomyces hominis*. *Science* 94:568, 1941.

MEDICAL PROGRESS

THE PLASMA PROTEINS: THEIR IMPORTANCE IN CLINICAL MEDICINE AND SURGERY*

CHARLES A. JANEWAY, M.D.†

BOSTON

DURING the past few years a great amount of effort has been devoted to studies of the plasma proteins in health and disease. With the development of satisfactory methods for the preservation of plasma, which has been of great importance in military medicine and which has made plasma widely available to practitioners, the need for an understanding of the functions of the different constituents of plasma is obvious. This report is intended to supplement Loeb's[1] excellent and comprehensive review on the plasma proteins, with a more detailed discussion of their functions and a consideration of methods for the treatment of various types of protein deficiency.

METHODS OF STUDY

Progress in the field of blood proteins, as in most other fields of medical research, is dependent on the chemist. Blood plasma is a complex fluid consisting of a mixture of crystalloid substances and protein in water. The proteins of the plasma comprise a large group of molecular species that differ over a wide range in chemical characteristics and physiological functions. The primary aim in the chemical study of these substances is to separate them into fractions of sufficient purity so that they may be accurately characterized chemically. This aim is now beginning to be realized[2] on a sufficiently large scale to make it possible to use these fractions extensively in the treatment and study of disease.

In making the different plasma proteins available in a highly purified state, the chemist is providing the clinician and the physiologist with a fundamental tool essential to the satisfactory study of their functions. The importance of having a plasma protein relatively pure is obvious from the standpoint of the therapy of a deficiency of that protein, but its importance for the controlled investigation of its functional significance cannot be overemphasized.

As Loeb pointed out, recent advances in the chemistry of the plasma proteins have been aided by the development of new analytical tools, although methods for the preparation of pure protein fractions in some cases antedated their use. The first of these, the ultracentrifuge, makes it possible to analyze proteins by means of their rate of sedimentation in a centrifuge rotating at a tremendously high rate of speed. The rate of sedimentation depends on the size and shape of the molecule. The second tool, the electrophoresis apparatus, enables the chemist to separate and analyze a mixture of proteins on the basis of their rates of migration in an electric field. This in turn depends on the size, shape and particularly the net charges of the respective molecules. Since the net charge depends on the hydrogen ion concentration of the buffer solution in which the protein is dissolved, it is essential always to know the pH, and particularly the type of buffer used in any analysis.

Tiselius, whose name is borne by the modern electrophoresis apparatus that he developed, divided the plasma globulins into three components — alpha, beta and gamma. Albumin migrates most rapidly, alpha globulin next, then beta globulin and fibrinogen and finally gamma globulin, which exhibits the slowest rate of migration in the electric field. In each of these electrophoretic components of plasma, as in the fractions prepared by salting out with different concentrations of neutral salts, there is not one protein, but a number of different proteins that happen to exhibit a common type of behavior under the particular conditions of the analysis, but that may be further separated under different conditions. The value of both ultracentrifugal and electrophoretic analysis depends to a large extent on the ease and accuracy with which the results can be read, which in turn are due to the fact that a complicated optical system devised for each makes it possible to record the results graphically.

These two tools, which analyze proteins on the basis of quite different attributes of the molecule, have been very useful as guides and checks on the more conventional and important methods of

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

*From the Department of Pediatrics, Harvard Medical School, the Department of Communicable Diseases, Harvard School of Public Health, and the Children's and Infants' hospitals.

†Assistant professor of pediatrics, Harvard Medical School and School of Public Health; visiting physician, Children's and Infants' hospitals.

separating proteins that depend on differences in solubility. A third tool, mentioned by Loeb, which has contributed much to this field, has been the development of exact immunochemical methods by Boyd[3] and Heidelberger.[4] None of these methods have any general application to clinical chemistry at the moment, because the apparatus is too expensive and because highly trained workers are needed to interpret the results, but they are mentioned in so many recent papers that a few words in this review seem justified.

Another method of analysis of proteins is the study of their composition in terms of their fundamental units, the amino acids. This is of great importance not only in determining the finer details of structure of the different protein molecules, but also in defining their nutritional value. Such a method of analysis, however, is one of the most laborious and difficult in the field of chemistry.

In clinical laboratories, several methods for determination of the plasma protein concentration have been used. The most accurate and widely used is that which makes use of their solubilities: that is, the salting out of various protein fractions by different concentrations of neutral salts, particularly sodium sulfate.[5] In this way the plasma is broken up into several conventional fractions, each of which contains a mixture of protein molecules of similar solubility.

In addition to this direct method, which has the great virtue of enabling one to determine not only the total protein content but also the amounts of albumin and globulin present in any plasma specimen, are a number of indirect methods for the determination of the protein content of plasma. One that has found widespread use because of its simplicity is the determination of plasma specific gravity, which in turn depends almost entirely on its protein content.[6, 7] Unfortunately, specific-gravity methods have one great defect: namely, that they fail to give any idea of the relative concentrations of different proteins in the plasma. Thus, it is possible to have a normal specific gravity with a very low plasma albumin level, owing to an associated increase in globulin concentration. In studying the progress of single cases, however, and particularly in following the acute changes in such conditions as burns and traumatic shock, this method has proved extremely useful and has a definite place in the laboratory technic of any hospital that handles acute surgical and medical emergencies.

A number of empirical tests that have been used in clinical medicine for varying periods of time depend on variations in the pattern of the plasma proteins. The most widely used of these is the sedimentation rate, which, as Fahraeus,[8] showed, depends not on changes in the red cells themselves but on changes in the menstruum in which they are suspended. Changes in the plasma influence the rate of aggregation of the red cells, and hence the size of the resulting particles, which, with the viscosity of the plasma itself, determines the rate of sedimentation or the extent of settling in a given period of time. Recent studies by Ham and Curtis[9] and others have shown that an increased sedimentation rate occurs when there is an increase of certain plasma globulins, particularly fibrinogen, and that it depends on alterations of the colloidal state of the plasma.[10]

Other reactions that have been used to detect increases in the globulin fraction or the presence of certain abnormal globulins are the formol gel, Takata–Ara, Weltman coagulation, cephalin flocculation and colloidal-gold tests. The studies of Kabat and his co-workers[11] indicate that the colloidal-gold activity of the cerebrospinal fluid from cases of syphilis of the central nervous system is associated with the presence of a gamma globulin fraction apparently derived from the central nervous system, since its relative concentration is much higher than in the serum. In normal spinal fluids the protein pattern reflects that of the serum, but the concentration is about one three-hundredth as great. A subsequent study has shown that the cephalin flocculation reaction, found by Hanger[12] to be positive in cases of hepatic damage and thus to be useful in distinguishing between obstructive and hepatogenous jaundice, is due to changes in the gamma globulin fraction of serum.[13] Unlike the colloidal-gold reaction, it is not inhibited by albumin. Tests that probably detect the presence of specific abnormal globulins that have not been isolated are the cold agglutinin test, recently advocated for the diagnosis of certain forms of atypical pneumonia,[14] and the Donath–Landsteiner test for the presence of the cold hemolysins that give rise to the syndrome of paroxysmal hemoglobulinuria of the syphilitic type.[15] It is to be hoped that further researches will reveal more exactly the nature of the disturbances in blood proteins that underlie these different reactions, thus greatly enhancing the value of these relatively simple and hence convenient tests.

The Clinical Significance of Different Plasma Proteins

Plasma Albumin

Chemical properties. The albumin molecule is smaller than most globulin molecules. It is more nearly spherical and carries a higher net charge.

Hence it moves with greater rapidity in an electric field, and also exerts the greatest osmotic pressure of the plasma proteins.[2] Solutions of concentrated human serum albumin are remarkably stable at moderately elevated temperatures, making it possible to issue concentrated albumin in liquid form for the armed forces [16, 17] It is this stability of the albumin and the importance of serum albumin in body economy that make aged liquid plasma[18] useful in the treatment of shock and hypoproteinemia, since the albumin it contains is presumably little altered by long periods of storage at room temperature, although many of its less stable globulin components have lost their physiologic activity.

Physiological functions. Serum albumin seems to perform two very important functions. In the first place, there is a constantly increasing body of evidence that serum albumin reflects changes in the protein nutrition of the whole body. Under conditions of protein starvation, as Weech[19] has shown, there is a steady fall in the serum albumin concentration of the plasma, whereas the globulin level is hardly disturbed at all. That this fall reflects a depletion of the protein stores of the whole body has been demonstrated clearly by a number of workers. In work on dogs, Elman and his group[20] and Whipple and his associates[21] have shown that in the treatment of hypoproteinemia only a small proportion of the protein that has been administered, and proved by nitrogen balance studies to be retained in the body, can be accounted for by the increase in circulating plasma protein, particularly albumin. The remainder is withdrawn into the tissues. Under conditions in which there is a marked loss of protein from the body, it is the serum albumin level in particular that usually reflects the depletion. In many cases, as, for example, in nephrosis, albumin is being lost more rapidly than other proteins.[22] Hypoproteinemia with protein loss is observed in patients with chronic draining infections, multiple paracenteses, proteinuria or chronic diarrheal disease, particularly when the protein intake is low. Under certain conditions, a low serum albumin may not necessarily reflect a generalized protein deficiency so much as a failure of the normal synthesis of serum albumin. This is particularly seen in conditions of hepatic failure, notably in cirrhosis of the liver, in which Patek and his group[23] have shown that even with high-protein diets and the maintenance of a positive nitrogen balance it is frequently impossible to elevate the serum albumin level.

Superficially there may seem to be some contradiction between the work of Weech, which emphasizes the nutritional importance of the albumin fraction only, and the work of Whipple and his colleagues, which shows that both albumin and globulin are produced rapidly by dogs whose protein stores have been depleted by a regime of repeated plasmaphoresis and a low-protein diet. Actually there is no discrepancy to be explained. Weech has produced hypoproteinemia by a process of protein starvation, thus allowing the dogs to exhaust their own stores of plasma protein-building material. Whipple and his group have produced hypoproteinemia by a combination of a low-protein diet with the active removal of large amounts of plasma protein from the dogs by bleeding and returning the cells to the circulation. Thus, the factor of loss of the whole plasma protein mixture is added to that of a low-protein diet. When both albumin and globulin are lost, both protein fractions are manufactured at a rate that is influenced by the available reserves and by the type and amount of dietary protein. Weech's experiments indicate that when the diet contains an amount of protein inadequate to repair the normal wear and tear of the tissues, serum albumin is gradually utilized for this purpose, thus suggesting that it is the more useful of the two fractions for supplying the needs of the tissues. Further studies on the relative importance of the different plasma protein fractions in supplying the needs of different tissues will undoubtedly be stimulated by investigations of the tissue proteins and by the availability of large amounts of purified plasma protein fractions. That there is a constant exchange of amino acids as well as of individual carbon, nitrogen and hydrogen atoms between both protein fractions of plasma and the tissues has been amply demonstrated by the brilliant work of Schoenheimer.[24]

The second significant function of serum albumin is the maintenance of plasma volume. The early studies of Starling[25] in this field indicated the importance of colloid osmotic or oncotic pressure of the plasma in retaining fluid within the circulation. Subsequent work has related the colloid osmotic pressure of the plasma chiefly to its content of serum albumin. Govaerts[26] introduced a formula for the calculation of osmotic pressure of the serum based on its content of albumin and globulin, and showed that when the oncotic pressure is below a certain critical level, edema is almost always present. The importance of hypoalbuminemia in edema and ascites is now well established by many clinical observations.[19] Recently Scatchard, Bachelder and Brown,[27] with access to pure solutions of albumin prepared by Cohn and his associates,[28] have demonstrated that 80 per cent of the colloid osmotic pressure of normal plasma is due to its albumin, which, however, makes up but 60 per cent of the total protein. Thus, 0.8 gm. of albumin is the equivalent of 1.0

gm. of a normal mixture of plasma proteins. It has likewise been demonstrated that the quantitative response to the injection of concentrated albumin solutions is what might be expected from these accurate in vitro measurements.[29]

Although albumin seems to behave in the human circulation as might be expected on the basis of its physicochemical properties, it should not be regarded as an inert substance trapped in the circulation like gum acacia. Rather, it is in a constant state of dynamic equilibrium with the tissue proteins. For example, shortly after the injection of acacia the concentration of serum albumin falls markedly, presumably to compensate for the increase in oncotic pressure produced by the acacia, which cannot be so readily removed from the circulation.[30] Furthermore, albumin, and to a lesser extent some of the other serum proteins, are not held completely within the blood vessels, but apparently do pass in small amounts across the capillary walls, as the extensive researches of Drinker[31] and Landis[32] have shown, and even perhaps across the glomerular capillaries, as the work of Dock suggests.[33] Plasma proteins that pass across the capillary wall into the tissue fluid, as well as other proteins derived from the tissues themselves, probably do not pass back directly into the capillaries but are returned to the circulation by the lymphatic system.[31]

Whereas serum albumin plays an important role in the regulation of blood volume, it is not the only factor concerned. If it were, the nephrotic patient would have virtually no circulating plasma, because of the extremely low levels of serum albumin in nephrotic plasma and its low oncotic pressure. Pressure within the tissues themselves, — which rises with the accumulation of edema fluid,[34] — the intake of salt and fluids,[35] the permeability of the capillary wall, and arterial and venous pressures, all play a role in the regulation of amounts of fluid held within and without the main circulation.

There is nothing to add to the discussion by Loeb[1] on the source of plasma albumin in the body. Considerable evidence implicates the liver and particularly the hepatic parenchymal cells as the main site of albumin manufacture, but it cannot be said that albumin is manufactured *only* by the liver.

Plasma Globulins

Although plasma albumin constitutes a relatively homogeneous group of closely related proteins, the plasma globulins are multiple and complex. As a group, they differ from albumin in their greater molecular asymmetry, lower net charge and, in most cases, larger molecular size.[36] The stability of most globulins is less than that of the albumins, but this is not universally true. In fact, one cannot generalize about the globulins, which are a large group of complex and very different proteins.

Whereas serum albumin is developed early in life, the pattern of serum globulins increases in complexity with growth and development and as a result of the contact of the organism with its environment. Thus, Rapoport and his co-workers[37] have recently reported on the plasma protein fractions in the neonatal period and infancy. They have shown that whereas both albumin and globulin concentrations of the plasma are somewhat lower shortly after birth and increase slowly throughout infancy, the increase in the globulin fraction is proportionately greater. How much of this is due to the normal processes of maturation and how much to the response to various antigenic stimuli is not yet clear. This relative hypoproteinemia of early infancy is of interest in relation to the ease with which edema develops in newborn infants shortly after delivery. The following discussion will be confined largely to the importance of the globulins from the functional point of view, which is of interest to the clinician, rather than to their chemical characteristics, which in many cases are still to be defined accurately.

Reactions of immunity. That antibodies are globulins is supported by abundant data derived from the study of both human and animal serums.[38] Much of the antibody globulin found in the plasma of the newborn infant is derived from its mother.[39] This may be acquired in two ways: by passage across the placenta from the maternal circulation, and by transfer in the colostrum. The latter route seems to be the sole method of transfer of antibodies in certain herbivorous animals such as the cow,[40, 41] in which the structure of the placenta is such that there is a far less intimate relation between maternal and fetal circulations than exists in the human placenta, with its very thin layer of syncytium and cells separating the two circulations. The placental route of transfer in human beings is almost certainly the more important of the two. Recent studies of the etiology of erythroblastosis fetalis indicate that the passage between the two circulations can be a two-way one, since the mother is immunized by cells derived from the fetus, and her antibodies then return to the fetal circulation, where they produce the destruction of fetal cells and the severe form of hemolytic anemia associated with erythroblastosis fetalis.[42]

The duration of this inherited placental immunity seems to vary in proportion to the concentration of antibody inherited. Most of this inherited antibody is lost at the end of six months, but during the first six months of life most infants

are protected from scarlet fever, diphtheria, poliomyelitis and measles, provided their mothers possess antibodies to these diseases.[39] On the other hand, infants possess little or no immunity against other diseases, such as pertussis, for which adults do not possess circulating antibodies in an appreciable concentration. It is in the age period from a few months to two years that the mortality of most infectious diseases is highest: that is, during the time between the loss of inherited immunity and the acquisition of active immunity as a result of outside stimuli. The antibody globulin pattern of the adult is gradually built up as a result of the repeated antigenic stimulation of frank infections, latent or unrecognized infections and artificial immunization. Before the age of six months, infants, like young rabbits, do not respond well to antigenic stimuli,[39] and it is for this reason that active immunization against pertussis, diphtheria and smallpox is usually deferred until the age of six months is reached.

Few specific antibody globulins have been characterized chemically, with the exception of those found in the serums of highly immunized animals, which have been found to be gamma globulins: that is, globulins that migrate slowly in the electric field. Methods for the detection of antibodies have been entirely nonchemical in the past, but with the development of quantitative immunologic technics, the chemist has gradually begun to invade the province of the immunologist.

Although antibodies are extremely useful in the diagnosis of many infectious diseases, and their presence in the serum usually indicates a state of resistance, their primary importance in bringing about the cure of specific infections is in many cases open to question. In general, passive immunization by the administration of sufficient preformed antibody is more universally effective in prevention than in the treatment of infectious disease. Thus, tetanus antitoxin can prevent tetanus when given in sufficient quantities, but its therapeutic effect is dubious. On the other hand, both diphtheria and scarlatinal antitoxins are unquestionably therapeutically effective when administered early in the disease, and the antibacterial serums developed against the pneumococcus[43] and the influenza bacillus[44] have proved their worth in the clinic. In such a disease as typhoid fever, and in most virus diseases, the administration of antibodies is ineffective as a form of treatment, possibly because the etiologic agent multiplies within the body cells,[45, 46] where it is protected from the action of the antibodies.

Most evidence indicates that the antibody globulins, or at least those globulins produced in response to antigens that gain access to the body from outside,* arise in the reticuloendothelial cells. Evidence for this view is not overwhelming but is extremely suggestive.[47]

Besides the antibodies, there are other globulin components of normal plasma that play a role in immune reactions. These are the fractions of *complement* or *alexin*, which are of protein nature. Complement has been divided into four components. Two protein components, the so-called "midpiece" and "endpiece," have been separated from guinea-pig serum by Pillemer, Ecker, Oncley and Cohn,[48] and from human serum by Ecker, Pillemer and their associates,[49] and have been shown to have mobilities that place them with the alpha and beta globulins. Further studies along these lines should help to elucidate this exceedingly complex field of immunology. There is little evidence on the source of complement, but it is known that this substance is regenerated very rapidly after depletion.[50] Although there can be no doubt of the importance of complement to in vitro immunologic tests, notably the complement-fixation reaction, there is far less evidence that complement plays any vital role in the resistance of the body to infection. Ham and Dingle[51] have shown that complement is apparently responsible for the hemolysis of a patient's own blood that occurs in paroxysmal nocturnal hemoglobinuria, in which it acts in conjuncton with an unidentified hemolysin. Complement action is also known to be essential to the Donath–Landsteiner reaction, and in all probability actually produces the hemolysis of the syphilitic type of paroxysmal hemoglobinuria, after the cells have been sensitized by the cold hemolysin. In both these instances, complement plays an adverse role in the body economy. In vitro it is known to enhance the speed of phagocytosis,[52] and it is essential to the destruction of gram-negative organisms by the bacteriolysins of the serum, as shown by Spink and Keefer[53] for the gonococcus, and by Fothergill and his co-workers[54] for *Haemophilus influenzae*.[54] In vitro bactericidal tests carried out in our own laboratory with the beta-hemolytic streptococcus indicate that complement is essential to the bactericidal action of whole blood,[55] as had been demonstrated in the case of the pneumococcus by Robertson and his associates.[56] In the case of both these gram-positive cocci, phagocytosis precedes the bactericidal effect. Its importance in vivo has not, however, been clearly shown, but is suggested by some work of Rutstein and his co-workers,[57] who found that in certain cases of pneumococcal pneu-

*The isohemagglutinins probably develop as a result of the maturation process and not in consequence of antigenic stimulation. Study of the chemical nature of these essentially normal antibodies, which are readily identified by their activity in agglutinating the red cells of persons of other blood groups, should be of great interest.

monia there seemed to be a partial deficiency of complement. That complement titers might fall during acute disease states in which an antigen-antibody reaction is probably taking place is suggested by the finding of low values in serum disease.[57, 58]

(To be concluded)

References

1. Loeb, R. F. Plasma proteins in health and disease. *New Eng. J. Med.* 224:980-987, 1941.
2. Cohn, E. J. Properties and functions of plasma proteins, with consideration of methods for their separation and purification. *Chem. Rev.* 28:395-417, 1941.
3. Boyd, W. C. *Fundamentals of Immunology*. 446 pp. New York: Interscience Publishers, Inc., 1943. Pp. 195-212, 388 and 389.
4. Heidelberger, M. Quantitative absolute methods in study of antigen-antibody reactions. *Bact. Rev.* 3:49-95, 1939.
5. Howe, P. E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood. *J. Biol. Chem.* 49:93-107, 1921.
6. Hamilton, W. F., and Barbour, H. G. Falling drop method for determining specific gravity. *J. Biol. Chem.* 69:625-640, 1926.
7. Kagan, B. M. Simple method for estimation of total protein content of plasma and serum. I. Falling drop method for determination of specific gravity. *J. Clin. Investigation* 17:369-372, 1938. II. Estimation of total protein content of human plasma and serum by use of falling drop method. *Ibid.* 17:373-376, 1938.
8. Fahraeus, R. Suspension stability of blood. *Physiol. Rev.* 9:241-274, 1929.
9. Ham, T. H., and Curtis, F. C. Sedimentation rate of erythrocytes. *Medicine* 17:447-517, 1938.
10. Ropes, M. W., Rossmeisl, E., and Bauer, W. Relationship between erythrocyte sedimentation rate and plasma proteins. *J. Clin. Investigation* 18:791-798, 1939.
11. Kabat, E. A., Moore, D. H., and Landow, H. Electrophoretic study of protein components in cerebrospinal fluid and their relationship to serum proteins. *J. Clin. Investigation* 21:571-577, 1942.
12. Hanger, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation* 18:261-269, 1939.
13. Kabat, E. A., Hanger, F. M., Moore, D. H., and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J. Clin. Investigation* 22:563-568, 1943.
14. Peterson, O. L., Ham, T. H., and Finland, M. Cold agglutinins (autohemagglutinins) in primary atypical pneumonias. *Science* 97:167, 1943.
15. Mackenzie, G. M. Paroxysmal hemoglobinuria: review. *Medicine* 8:159-191, 1929.
16. Newhouser, L. R., and Lozner, E. L. Use of human albumin in military medicine. III. Standard Army-Navy package of serum albumin human (concentrated). *U. S. Nav. M. Bull.* 40:796-799, 1942.
17. Kendrick, D. B., Jr., Reichel, J., Jr., and McGraw, J. J., Jr. Human serum albumin concentrated: clinical indications and dosage. *Army M. Bull.* 68:107-112, 1943.
18. Newhouser, L. R., and Lozner, E. L. Practical considerations in therapeutic use of blood derivatives. *New Eng. J. Med.* 228:671-674, 1943.
19. Weech, A. A. Significance of albumin fraction of serum. *Bull. New York Acad. Med.* 15:63-91, 1939.
20. Sachar, L. A., Horvitz, A., and Elman, R. Studies on hypoalbuminemia produced by protein-deficient diets. I. Hypoalbuminemia as a quantitative measure of tissue protein depletion. *J. Exper. Med.* 75:453-459, 1942.
21. Madden, S. C., and Whipple, G. H. Plasma proteins: their source, production and utilization. *Physiol. Rev.* 20:194-217, 1940.
22. Luetscher, J. A., Jr. Electrophoretic analysis of plasma and urinary proteins. *J. Clin. Investigation* 19:313-320, 1940.
23. Post, J., and Patek, A. J., Jr. Serum proteins in cirrhosis of liver. II. Nitrogen balance studies on five patients. *Arch. Int. Med.* 69:83-89, 1942.
24. Schoenheimer, R. *Dynamic State of Body Constituents*. 78 pp. Cambridge: Harvard University Press, 1942.
25. Starling, E. H. On adsorption of fluids from connective tissue spaces. *J. Physiol.* 19:312-326, 1896.
26. Govaerts, P. Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedèmes. *Bull. Acad. roy. med. de Belgique* 7:356-373, 1927.
27. Scatchard, G., Bachelder, A. C., and Brown, A. Unpublished data.
28. Cohn, E. J., Oncley, J. L., Strong, L. E., Armstrong, S. H., Ferry, R. M., and Hughes, W. L., Jr. Properties and functions of the purified proteins of animal and human plasma. Chap. 20. In Mudd, S., and Thalhimer, W., *Blood Substitutes and Blood Transfusion*. 407 pp. Springfield, Illinois: Charles C Thomas, 1942.
29. Heyl, J. T., and Janeway, C. A. Use of human albumin in military medicine. I. Theoretical and experimental basis for its use. *U. S. Nav. M. Bull.* 40:785-791, 1942.
30. Heckel, G. P., Erickson, C. C., Yuile, C. L., and Knutti, R. E. Blood plasma proteins as influenced by intravenous injection of gum acacia. *J. Exper. Med.* 67:345-360, 1938.
31. Drinker, C. K., and Yoffey, J. M. *Lymphatics, Lymph, and Lymphoid Tissue: Their physiological and clinical significance*. 406 pp. Cambridge: Harvard University Press, 1941.
32. Landis, E. M., Jonas, L., Angevine, M., and Erb, W. Passage of fluid and protein through human capillary wall during venous congestion. *J. Clin. Investigation* 11:717-734, 1932.
33. Dock, W. Proteinuria and associated renal changes. *New Eng. J. Med.* 227:633-636, 1942.
34. Warren, J. V., Merrill, A. J., and Stead, E. A., Jr. Rôle of extracellular fluid in maintenance of normal plasma volume. *J. Clin. Investigation* 22:635-642, 1943.
35. Stewart, J. D., and Rourke, G. M. Effects of large intravenous infusions on body fluid. *J. Clin. Investigation* 21:197-205, 1942.
36. Cohn, E. J. Plasma proteins: their properties and functions. *Tr. & Stud. Coll. Physicians Philadelphia* 10:149-162, 1942.
37. Rapoport, M., Rubin, M. I., and Chaffee, D. Fractionation of serum and plasma proteins by salt precipitation in infants and children. *J. Clin. Investigation* 22:487-498, 1943.
38. Boyd.[3] Chap. 2. Pp. 21-82.
39. McKhann, C. F., and Kapnick, I. Immunity and susceptibility to disease in early infancy. *J. Pediat.* 13:907-918, 1938.
40. Smith, T., and Little, R. B. Cow serum as substitute for colostrum in new-born calves. *J. Exper. Med.* 36:453-468, 1922.
41. Schneider, L., and Szathmáry, J. Ueber die Immunität der neugeborenen Säugetiere. *Ztschr. f. Immunitätsf. u. exper. Therap.* 94:458-465, 1938.
42. Levine, P., Burnham, L., Katzin, E. M., and Vogel, P. Role of isoimmunization in pathogenesis of erythroblastosis fetalis. *Am. J. Obstet. & Gynec.* 42:925-937, 1941.
43. Finland, M. Controlling clinical therapeutic experiments with specific serums. *New Eng. J. Med.* 225:495-506, 1941.
44. Alexander, H. E., Ellis, C., and Leidy, G. Treatment of type specific *Hemophilus influenzae* infections in infancy and childhood. *J. Pediat.* 20:673-698, 1942.
45. Goodpasture, E. W. Immunity to virus diseases: some theoretical and practical considerations. *New Eng. J. Med.* 222:901-910, 1940.
46. Adams, J. W., Jr. Intracellular bacilli in intestinal and mesenteric lesions of typhoid fever. *Am. J. Path.* 15:561-566, 1939.
47. Sabin, F. R. Cellular reactions to dye-protein with concept of mechanism of antibody formation. *J. Exper. Med.* 70:67-82, 1939.
48. Pillemer, L., Ecker, E. E., Oncley, J. L., and Cohn, E. J. Preparation and physicochemical characterization of serum protein components of complement. *J. Exper. Med.* 74:297-308, 1941.
49. Ecker, E. E., Pillemer, L., Seifter, S., Dozois, F. F., and San Clementi, C. L. Human complement. *Science* 98:43, 1943.
50. Wasserman, P. Rate of complement formation in dogs. *J. Immunol.* 40:281-287, 1941.
51. Ham, T. H., and Dingle, J. H. Studies on destruction of red blood cells. II. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: certain immunological aspects of hemolytic mechanism with special reference to serum complement. *J. Clin. Investigation* 18:657-672, 1939.
52. Ward, H. K., and Enders, J. F. Analysis of opsonic and tropic action of normal and immune sera based on experiments with pneumococcus. *J. Exper. Med.* 57:527-547, 1933.
53. Spink, W. W., and Keefer, C. S. Studies of gonococcal infection. I. Study of mode of destruction of gonococcus in vitro. *J. Clin. Investigation* 16:169-176, 1937.
54. Dingle, J. H., Fothergill, L. D., and Chandler, C. A. Studies on Haemophilus influenzae. III. Failure of complement of some animal species, notably guinea pig, to activate bactericidal function of sera of certain other species. *J. Immunol.* 34:357-391, 1938.
55. Janeway, C. A., and Chandler, C. A. Unpublished data.
56. Robertson, O. H., Sia, R. H. P., and Cornwell, M. A. Activating effect of fresh normal serum on pneumococcidal-promoting action of antipneumococcus serum, Type I. *J. Immunol.* 19:429-443, 1930.
57. Rutstein, D. D., and Walker, W. H. Complement activity in pneumonia. *J. Clin. Investigation* 21:347-352, 1943.
58. Miura, T. Untersuchungen über die experimentelle Serumkrankheit. *Tr. Soc. path. jap.* 30:378-386, 1940.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 29451

PRESENTATION OF CASE

A forty-nine-year-old mechanic entered the hospital because of substernal pain of one day's duration.

The patient had been in apparent good health until five years before admission, at which time, during the course of a physical examination, an aortic diastolic murmur was discovered. No history of a chancre could be obtained but the suspicion of syphilis was substantiated, however, by a positive serologic test. He was treated regularly for two years, medication consisting of intramuscular injections as well as about six intravenous injections. No other treatment was given until the month before entry when he received five intramuscular injections. Eighteen months before entry he noted moderate fatigue but continued working at his heavy job. One day, about three months before admission, he developed severe crushing substernal pain early in the morning, while sitting and waiting to go to work. Bromoseltzer gave some relief. He worked till the noon hour of that day. The pain recurred while eating lunch. His pulse was said to have been fast. The pain subsided after passing gas by rectum several times after one hour. Five weeks before entry he had recurrence of the same pain while eating; this lasted one or two hours. He continued to work for four days without distress but awakened each night with severe pain and dyspnea. He had difficulty in sleeping for three or four nights because of orthopnea. From this time on he experienced some pain on exertion and eventually stopped working. The blood pressure was said to have been "204 systolic." The radial pulse was 84, but at the "base of the heart" the rate was found to be 160. He was given quinidine, and in about thirty-six hours the radial pulse rate and the heart rate at the base of the heart were said to have corresponded. An electrocardiogram taken two weeks before admission showed a rate of 90, left-axis deviation, depressed ST segments in Leads 1 and 2 and inverted T waves in Lead 1. Moderate numbers of ventricular premature beats were present, at times in pairs, and also occasional auricular premature beats. The day before entry he awoke after two hours of sleep to void. He did not return to bed, and while sitting, he developed the same substernal pain, which was so severe as to necessitate a hypodermic injection by his physician. The day of admission he experienced substernal discomfort on the way to the hospital. He was said to have had no digitalis for one week, and before then one small tablet a day, after taking one three times a day for two weeks.

He had had gonorrhea twenty-six years before admission.

Physical examination showed an obese, apparently healthy man. The pupils were equal and reacted to light. An arterial pulse was visible in the neck. The heart was enlarged to the left, the apex being 13 cm. from the midsternal line in the fifth interspace. The sounds were of fair quality and regular. There was a blowing aortic diastolic murmur and a Grade 2 aortic systolic murmur. The pulse was Corrigan in type. The lungs were clear. The abdominal examination was negative. The deep tendon reflexes were active.

The blood pressure was 180 systolic, 55 diastolic. The temperature was 98.6°F., the pulse 96, and the respirations 25.

Fluoroscopic examination revealed a large transverse heart with a base measuring 9.5 cm. The heart width measured 15.7 cm., as compared with 23.5 cm. for the inner diameter of the chest. In the left anterior oblique view there was a curve in the midthird of the cardiac silhouette that extended out 3 or 4 cm.

The patient was given nitroglycerin on admission, and this was repeated two and four hours later, giving a total of three doses. There was some relief from pain, but morphine was also given because of the severity of the pain. The patient was apprehensive and tense and ate sparingly; he was, however, able to sleep. He received two 0.2-gm. doses of digitalis. Fifteen hours after admission, at about 5:00 a.m., he signaled for the nurse, who found him with his head back, gasping, unconscious and pulseless. He died twenty minutes later.

DIFFERENTIAL DIAGNOSIS

DR. PAUL D. WHITE: We can assume that this patient had aortic regurgitation. At the age of forty-five, aortic regurgitation means either rheumatic heart disease, which is more probable in this part of the world, or aortic syphilis, which is less common here than in many other places. It rarely means anything else, but we did see a patient at medical grand rounds this morning with aortic regurgitation due apparently to hyperten-

*On leave of absence.

sion — that might be called functional regurgitation, without aortic-valve disease. In the record of this case there is no statement of early dyspnea, nor did the patient complain of paroxysmal tachycardia. Of course, paroxysmal tachycardia due to coronary or myocardial insufficiency may precipitate symptoms not previously present. We cannot be sure of what happened at first in this patient.

When pain did begin its duration was intermediate between what we usually find with angina pectoris on effort (or decubitus) and what we usually find with myocardial infarction.

It is distinctly unusual, although possible, for pain due to coronary insufficiency to occur first at rest and only later on effort. Almost invariably it is the other way around, some weeks, months or years elapsing before the pain finally occurs at rest. Here we have the reverse. I expect that the description of the pain would have been the same throughout. I assume that it was substernal oppressive pain. It is said that the radial pulse rate was 84, but that at the base of the heart the rate was 160. I do not know what was meant by that. There is no further description. Was the heart rate regular? It is important to determine whether the patient had paroxysmal fibrillation, which can give a heart rate of 160 and a radial rate of 84 — a very large pulse deficit. Although unusual in this kind of patient, it is possible. It is unlikely that a coupled rhythm would have caused every other beat to have been premature, thus failing to reach the wrist; a bigeminal rhythm is rare with a rate as fast as 160. I do not believe that we can be quite sure what did happen, but the best bet is tachycardia with auricular fibrillation; with tachycardia of other sorts a pulse deficit of this degree usually does not occur.

Quinidine usually is given for arrhythmia, sometimes for tachycardia. Perhaps it was given for both in this patient. Whether the rhythm became normal as a result of quinidine or spontaneously we cannot be sure. There was some arrhythmia later, with auricular premature beats; hence the patient might readily have previously had an auricular tachycardia. Otherwise the electrocardiogram is simply characteristic of a big left ventricle from any cause. Such a big left ventricle is due most commonly either to hypertension or to aortic-valve disease. We know that the patient had aortic regurgitation, and so that fits best — namely, a big heart with aortic regurgitation. Coronary heart disease is one other possibility, but we do not as a rule find left-axis deviation with uncomplicated coronary heart disease. He may have had a combination of heart diseases. He had a systolic blood pressure of 204. There is no clear indication, however, from this electrocardiographic record of any fresh myocardial infarct. That point is rather important because from the history it is possible that he might have had several myocardial infarcts. Depressed ST segments do not have the same significance from the standpoint of acute myocardial damage as elevated segments, which in Leads 1 and 2 or in Leads 2 and 3 present reasonable evidence of acute myocardial infarction. We find no note of precordial leads, which would have been helpful in such a problem.

DR. BENJAMIN CASTLEMAN: They were not taken.

DR. WHITE: There is a possibility of some digitalis effect in the electrocardiogram, although the patient had not had a great deal of digitalis.

This man's height and weight are not given, but obviously the apex impulse was a long distance out. We can assume from physical examination that he had a very large heart.

I should have liked to have a grading of the diastolic murmur, as well as of the systolic. Perhaps it was Grade 3 or 4, somewhat louder relatively than the systolic murmur and a little more in keeping with aortic regurgitation and dilatation of the aorta than with rheumatic, syphilitic or calcareous aortic stenosis. The findings would have been reversed with a loud (Grade 4) aortic systolic murmur, and perhaps a Grade 2 diastolic murmur, if the case were one of rheumatic aortic stenosis. The Corrigan pulse is further evidence of free aortic regurgitation.

The deep tendon reflexes were active. It does not look as if the patient had any obvious evidence of syphilis of the central nervous system to go with the aortic syphilis; both are often present in the same patient.

We have not two readings of the diastolic pressure, which is sometimes recommended in cases of aortic regurgitation. There may be quite a difference between the sound changes in trying to determine the diastolic level. It is often wise, especially in aortic regurgitation, to record two readings. If the sound changes and disappears at about the same time one reading is enough. Not infrequently one will get a diastolic reading of 40 as the sound changes, and zero when it disappears. No one knows which is correct, so far as I am aware. Here we have the one reading of 55; quite likely there was a distinct change in note at that point.

"Fluoroscopic examination revealed a huge transverse heart, with a base measuring 9.5 cm." The base should be much wider to be called wide, if it is the width of the heart in the anteroposterior view that is meant, but if this refers to the cardiac pedicle, — that is, the shadow of the great vessels, — 9.5 cm. is distinctly wider than normal. The width across the great vessels is normally 6 or 7 cm.

"The heart width measured 15.7 cm., as compared with 23.5 cm. for the inner diameter of the

chest." With reference to the transverse diameter of the heart, the normal in a patient of this size is about 12.5 cm., so that there was at least 3 cm. of enlargement by x-ray.

Now we come to one of the oddities of the case. Everything has gone along easily up to this point. "In the left anterior oblique view there was a curve in the midthird of the cardiac silhouette that extended out 3 or 4 cm." That is evidently something unusual. There is no statement about the anteroposterior view.

DR. CASTLEMAN: No films were taken.

DR. WHITE: Then this must have been a fluoroscopic observation; but there is no statement whether the bulge was in front or in back, whether it pulsated or what its action was.

DR. CASTLEMAN: There is no further statement.

DR. WHITE: The point is rather important. I think that fluoroscopy by ourselves might have been helpful in our present dilemma.

This was not an abrupt death — that is, one due to acute coronary insufficiency, such as we find with ordinary angina pectoris and sometimes even with coronary thrombosis. A tamponade or a coronary occlusion could explain it.

Regarding the diagnosis, the presence of both coronary and myocardial insufficiency with pain and dyspnea in a man in the forties with a history of venereal disease, a positive serologic reaction, fairly free aortic regurgitation, a big left ventricle and aorta and early death, indicates almost certainly the presence of syphilitic aortitis with aortic regurgitation, left ventricular weakness and partial occlusion of the coronary ostia. As a matter of fact this history is almost too perfect for syphilitic aortitis with involvement both of the valve and of the coronary ostia. In such cases it is common to have both dyspnea and pain, and the pain is likely to be just as atypical as this — that is, atypical for coronary heart disease, either angina pectoris or myocardial infarction, the pain coming as it did for an hour at a time and not leaving any distinct trace on the electrocardiogram. The only real oddity is the unusual heart shadow by x-ray. It is not quite described as a bulge, but I suppose it would be if it measured 3 to 4 cm. in depth. It is important to remember that the aorta starts in the middle of the heart shadow. The beginning of the aorta cannot be seen in any view by x-ray. The first 2 or 3 cm. are buried in the heart shadow, almost in the center of the heart. Thus some lesion related to the base of the aorta would be the best bet for this unusual shadow. What could it be? An aneurysm at the root of the aorta is, I suppose, the best explanation of that shadow — an aneurysm possibly involving a sinus of Valsalva and extending out in one direction or another or even located just above the sinuses of Valsalva. An aneurysm sometimes presents itself some distance from the site of origin. A myocardial aneurysm of the left ventricle is lower than this bulge in position and so is unlikely here.

DR. CASTLEMAN: Dr. Currens is here and can answer your questions about the fluoroscopy.

DR. WHITE: How would you describe the bulge, Dr. Currens? Did it pulsate?

DR. JAMES CURRENS: It did not seem to pulsate any more than the rest of the aorta. If there was any pulsation it was transmitted. It was fairly round in contour, that is, it was regular in contour and did not extend out necessarily as a definite discrete mass.

DR. WHITE: Did it seem to be a part of the heart shadow? Could you distinguish it from the rest of the heart shadow except as it came out beyond it?

DR. CURRENS: No.

DR. WHITE: Was it anterior or posterior?

DR. CURRENS: Anterior. It seemed to be above the heart. It was in the region of the aorta rather than that of the heart.

DR. WHITE: It says here that it was in the middle third, but it was probably in the upper third too.

DR. CURRENS: Between the middle and upper thirds, I should say.

DR. WHITE: Could you see the bulge in the anteroposterior view?

DR. CURRENS: Yes; but not nearly so well as in the left anterior oblique view.

DR. WHITE: And the heart otherwise was large? There was no engorgement of the lung hilar shadows?

DR. CURRENS: Not particularly.

DR. WHITE: One other site for a syphilitic aneurysm in that region, which I have never encountered myself, but which is on record, is an aneurysm at the beginning of one of the coronary arteries. However, that is an extreme rarity. When the coronary arteries are involved, they are usually atherosclerotic. They may once in a while be invaded by a dissecting aneurysm of the aorta. There are two cases with involvement of the coronary artery itself without dissection of the aorta that we have tucked away to report sometime. In these cases there was rupture of the coronary artery and hemopericardium secondary to dissection of the wall of the artery. One of them was that of a patient with recent or fresh coronary thrombosis. A definite bulge of the heart shadow could not have been seen by x-ray in those cases.

The other question here concerns the matter of death. If this aneurysm was located in this region, how did the patient die? It is common for a patient with syphilitic aortitis to die by rupture of the aneurysm into either the pleural cavity or the pericardium. It would be quite consistent with

the story here for an aortic aneurysm near the mouth of the aorta to rupture into the pericardium with death in twenty minutes or so. That all seems too easy, however, except for the unusual position of the bulge, which might nevertheless have been an aneurysm.

I have put down other less probable possibilities, but I believe that we should take the diagnosis that I have just presented as the most likely, even though it may not be correct. Syphilitic aortitis plus coronary heart disease could have been the answer — that is, independent conditions, the coronary heart disease having resulted in death.

A hypertensive aorta with dissection into the sinuses of Valsalva, with or without aortitis, and a final rupture into the pericardium might have been the answer. Or even rheumatic heart disease or subacute bacterial endocarditis could explain the aortic regurgitation, with syphilis of the aorta on the side. Neoplasm of the heart is another odd condition that could have been present, or a congenital aneurysm of a sinus of Valsalva. A congenital defect superimposed on a bicuspid aortic valve has been described by Maude Abbott,[1] in which there may be a large sac extending out from the base of the aorta and involving a sinus of Valsalva with dissection of the wall and rupture into the pericardium. If that were present here, and were not due to syphilis, it would be in addition to the syphilitic aortitis.

I think that, despite all these other possibilities, we are probably justified, with what we have here, in diagnosing simply aortic syphilis with aortic regurgitation, marked cardiac enlargement, coronary insufficiency secondary to the syphilitic involvement of the aorta involving the ostia of the coronaries, and an aneurysm at the mouth of the aorta, perhaps involving a sinus of Valsalva, with rupture into the pericardium. Sudden death is possible in syphilitic cases without rupture of an aneurysm, but such a death would be more sudden than is stated here.

Clinical Diagnoses

Syphilis, cardiovascular, with aortic regurgitation and aneurysm of the ascending aorta.
Congestive heart failure.

Dr. White's Diagnoses

Syphilitic aneurysm of aorta, with rupture into the pericardium.
Hemopericardium, with cardiac tamponade.
Syphilitic aortitis, with aortic regurgitation and with involvement of coronary ostia.
Coronary insufficiency.
Cardiac hypertrophy.

Anatomical Diagnoses

Dissecting aneurysm of ascending aorta, with rupture into the pericardium.
Hemopericardium, with cardiac tamponade.
Syphilitic aortitis, with aortic insufficiency.
Cardiac hypertrophy, hypertensive.

Pathological Discussion

Dr. Castleman: At autopsy this man had a tremendous pericardial sac that was filled with about 500 cc. of blood producing obvious cardiac tamponade, which was the immediate cause of death. Within the pericardium we found a large aortic aneurysmal sac that contained a fair amount of blood clot, both old and new. This corresponded to the bulge observed fluoroscopically. When the aorta was opened there was obvious evidence of syphilitic aortitis throughout its entire length, with all the classic findings — stellate scarring, linear tree-barking and so forth. About 2 or 3 cm. above the aortic valve was a horizontal rent in the intima communicating with the aneurysmal sac, which was within the media of the aorta. This sac extended distally for 6 or 7 cm. to the opening of the innominate artery and down to the base of the heart, but did not reach the level of the coronary mouths. This sac was therefore a dissecting aneurysm of the aorta that had dissected for a relatively short distance.

I believe that three months before entry he had the initial intimal tear, and because of the syphilitic scarring in the media the progress of the dissection was slow and stopped at the arch, in contrast to the usual rapid dissection through the arch and down into the abdominal aorta. The pressure in the aneurysm increased, since blood was getting in but could not get out, and eventually produced external rupture and death.

Dr. White: How far down did the syphilitic process extend?

Dr. Castleman: It extended down to the aortic valve, but the coronary mouths were not involved. The aortitis had produced slight but definite separation of the cusps at their commissures, which accounts for the regurgitation. There was little coronary sclerosis.

Dr. White: How much did the heart weigh?

Dr. Castleman: The heart was huge, weighing about 900 gm., and was hypertensive in type.

Dr. White: The patient had had quite a number of attacks of pain. Do you think he tore his aorta every time?

Dr. Castleman: No; I think that the distention of the aneurysm as it enlarged was enough to produce pain.

DR. WHITE: It is possible to have angina pectoris when an enlarged heart has a wall so thick that it is not receiving enough blood through the coronary circulation, even though everything is open. Thus angina pectoris may occur without coronary heart disease, due to relative coronary insufficiency. That could be a plausible explanation of much of the pain here. The patient did have hypertension, of course, which helps a little toward the diagnosis of dissecting aneurysm. Do you remember, Dr. Castleman, that in the series of dissecting aneurysms that Glendy, you and I[2] reported the history was generally different from that of this case with respect to pain — usually there was one extremely severe attack of pain at the time of the first rupture and then a few hours, days or weeks later there occurred another attack of pain with death, without these recurrent pains. This case is unusual.

DR. CASTLEMAN: Yes; I think the aneurysm was being gradually built up.

DR. WHITE: But then so were the others.

DR. CASTLEMAN: They were much longer aneurysms, extending all the way down the aorta, and without the increased tension that you have here in the localized dissection.

DR. CURRENS: In light of the anatomic findings this case is of considerable interest to me. The late Dr. Soma Weiss in discussing dissection of the aorta cited dissecting aneurysms that dissect up to a region of syphilitic aortitis and then stop. He had one or two cases of this nature, and it was his impression that syphilis actually predisposed against dissecting aneurysm. The case under discussion is an exception to this thesis.

DR. WHITE: I am impressed by the occurrence of dissection of the aortic wall in just that part of the thoracic aorta — the ascending portion — in which the syphilitic process is the most active. This is in contrast to a few nonsyphilitic cases that I have seen in which the dissection of the aortic wall did stop at the arch because of the marked calcification of the entire descending aorta, whose wall was too hard to dissect. In this case the aortitis may have favored the dissection.

DR. CASTLEMAN: I can recall one case of dissecting aortic aneurysm in which the dissection was apparently stopped by syphilitic scarring in the media.[3]

REFERENCES

1. Abbott, M. E. *Atlas of Congenital Cardiac Disease*. 62 pp. New York: American Heart Association, 1936. P. 18.
2. Glendy, R. E., Castleman, B., and White, P. D. Dissecting aneurysm of aorta: clinical and anatomical analysis of nineteen cases (thirteen acute) with notes on differential diagnosis. *Am. Heart J.* 13:129-162, 1937.
3. Case 27302. Case records of Massachusetts General Hospital. *New Eng. J. Med.* 225:155-159, 1941.

CASE 29452

PRESENTATION OF CASE

A nine-year-old schoolgirl entered the hospital because of a "stuffed-up nose," coryza, fever and joint pains of six days' duration.

The patient had been in good health until about two weeks before entry, when she developed a cold that "never came to a head." There was no fever or loss of appetite. She felt well. Two days prior to entry she complained of being very cold. Her feet hurt when she walked. Her temperature was 103°F. A systolic murmur was heard for the first time by the family physician. The white-cell count was 18,500, with 77 per cent neutrophils. Urinalysis was negative. The family physician placed her on sulfadiazine, of which she received 160 gr. (nearly 11 gm.) up until the time of admission. The fever, however, persisted. Her appetite became poor but there was no vomiting or diarrhea. There was pain in the right foot and elbow, the neck and the shoulders, but no definite swelling or redness was seen. Motion in the legs and arms was limited. The day before entry she had several slight nosebleeds, and a moderately severe one on the day of admission. The pain shifted to the left elbow and midarm. On the day of admission she coughed up mucus and blood clots, which appeared to come from the pharynx.

Her tonsils and adenoids had been removed a year prior to admission. She had had measles, scarlet fever, chicken pox, German measles and whooping cough earlier in life. At seven years of age she had had "hives" twice, possibly caused by oatmeal.

Physical examination showed a well-developed and well-nourished child in no distress. Both eardrums were dull and slightly injected. Some blood-stained crusts were seen in the nostrils but no sinus tenderness could be elicited. The posterior cervical lymph nodes were slightly enlarged. The heart was of normal size. The sounds were of good quality and regular; there were no thrills. A blowing systolic murmur was heard at the apex, and a short systolic blow at the pulmonic area. The pulmonic second sound was greater than the aortic. There was difficulty extending the left arm completely; the pain could be localized at the elbow and in the midarm.

The blood pressure was 110 systolic, 72 diastolic. The temperature was 104.2°F., the pulse 110 and the respirations 30.

The blood showed a hemoglobin of 14.5 gm. and a white-cell count of 15,000, with 85 per cent neutrophils. The urine showed a + test for albumin but was otherwise negative.

X-ray examination of the chest revealed slight increased density of the right lung, suggesting

early consolidation of the right lower lobe. The lung markings extending up from the right hilus were somewhat prominent. There was an area of calcification overlying the anterior end of the fourth rib on the left. Examination of the air sinuses was negative. Tuberculin tests were negative in dilutions of 1:1000 and 1:100. An electrocardiogram showed normal rhythm, with a rate of 105, a P-R interval of 0.13 second, upright T waves in Leads 1 and 2, a diphasic T_3. A throat culture gave a few colonies of beta-hemolytic streptococci. Two blood cultures were negative. The sedimentation rate at fifteen-minute intervals was 6, 48, 53 and 55 mm.

The child was placed on sulfadiazine for three days, receiving a total of 11 gm. The blood sulfadiazine on the second hospital day was 8.7 mg. per 100 cc. The temperature remained elevated, ranging between 101 and 104°F.; the pulse was between 100 and 130, and the respirations between 20 and 25. On the seventh hospital day the red-cell count was 3,240,000, the hemoglobin 8.8 gm. and the white-cell count 14,100. The joint pains had disappeared, but the girl appeared listless, apathetic and anorexic. She was placed on aspirin, with a sudden drop of temperature to normal and of pulse to 90 after an initial dose of 25 gr. From that day on she received 60 to 65 gr. of aspirin daily. The temperature usually remained below 101°F., with only two spikes to 102, and the pulse was about 110. On the eleventh hospital day a loud friction rub was heard along the sternum. The apical blowing systolic murmur was well transmitted. The apical impulse was 3 cm. outside the midclavicular line in the fifth interspace. The rhythm, however, was regular.

On the following week she complained of dyspnea associated with atmospheric humidity. On the sixteenth hospital day she was pale and the heart was not enlarged, but the sounds were of poor quality. The rate was 116. The systolic murmur was coarse, and the friction rub was harsher than it had been. The liver edge could be palpated one fingerbreadth below the costal border. On the nineteenth hospital day, the neck veins appeared distended and the jugular pulsations were increased. The girl was dyspneic and cyanotic, and she was given 1 gr. of digitalis three times a day. On the twentieth day, she became semistuporous and incontinent. Respirations became labored, the pulse weak, and the heart sounds less audible. The following day the temperature rose to 105.5°F., the pulse to 155, and the respirations to 43 and the child died.

Differential Diagnosis

Dr. Ann G. Kuttner*: The striking thing about this child's initial upper respiratory infection is that it was extremely mild and that the patient did not seem seriously ill. Eight days later she began to have joint pains, which increased in severity. On the twelfth day fever and leukocytosis were also present. The family physician suspected a bacterial infection and gave the patient sulfadiazine. The development of migratory joint pains severe enough to restrict motion accompanied by fever and leukocytosis is characteristic of rheumatic polyarthritis.

The past history is of interest in that the patient had had scarlet fever. Most students of rheumatic fever agree that, with the exception of scarlet fever, the common childhood diseases have little influence either on the onset or course of the disease. Many children develop their first rheumatic manifestations following scarlet fever, and patients who have had rheumatic fever previously often develop relapses following this disease. It is extremely interesting that during this war there has been a marked incidence of rheumatic fever and heart disease following outbreaks of scarlet fever in various Army and Navy camps.

The course of this child's illness strongly suggests an acute attack of fulminating rheumatic fever. The onset with an upper respiratory infection so mild that it might easily be overlooked or forgotten is extremely common. I believe that if a throat culture had been taken at the time of the initial "cold," Group A beta-hemolytic streptococci would have been isolated.

The second feature that is typical is the latent period of approximately eight days between the initial symptoms of the upper respiratory infection and the appearance of rheumatic manifestations. This latent period may vary from one to three or four weeks, with an average length of about fourteen days. Characteristic rheumatic symptoms, migratory joint pains accompanied by fever and leukocytosis then developed.

The unusual feature in this case is that death apparently occurred during the first attack. Patients may die during the first attack but it is uncommon and usually occurs in a child somewhat younger than this patient. I think, therefore, it is of interest to scrutinize the history. Unfortunately no details are given regarding the attack of scarlet fever. I should like to know whether the patient had any joint pains or symptoms suggesting cardiac involvement at that time. I should also like to know whether there were any special indications for the tonsillectomy that was performed a year before admission.

Dr. Benjamin Castleman: Nothing further is stated in the record.

Dr. Kuttner: Because of the close association between streptococcal upper respiratory infections and rheumatic fever, it was hoped that the sulfonamide drugs would prove effective in this disease.

*Lecturer, Department of Bacteriology, Harvard Medical School.

But just the contrary has been found.[1, 2] Most observers agree that during the acute stages of rheumatic fever the sulfonamide drugs not only fail to benefit the patient, but the rheumatic symptoms may be aggravated by these drugs. I have not been convinced that the symptoms really were aggravated in the few cases in which I have tried it, but there certainly is no question that it does not benefit the patient.

In this patient the clinical picture on admission was somewhat puzzling. An x-ray film of the chest suggested early consolidation of the right lung. Sulfadiazine was therefore continued for three days, but the patient failed to improve. On the other hand salicylates given on the seventh day elicited a favorable response. A friction rub developed on the eleventh day and the heart was found to be somewhat enlarged, probably owing to a slight effusion. On the sixteenth day, when the friction rub became harsh, no cardiac enlargement was observed. The heart sounds then became progressively feebler, and it seems likely that a thick pericardial exudate had developed.

In my opinion the clinical diagnosis is acute rheumatic fever, pericarditis with a bread-and-butter exudate and little or no effusion, and rheumatic heart disease with mitral regurgitation. I suspect that in addition to the acute lesions, older lesions might also have been present, indicating that this was not the first attack of rheumatic fever.

Dr. Paul D. White: I was asked to see this youngster a few days before she died, chiefly to aid in the question of differential diagnosis between pericarditis and cardiac dilatation as the cause of the congestion that she showed. I can well recall having occasionally attempted to tap the pericardium of such a patient and almost always failing to get any appreciable amount of fluid, and later finding at post-mortem examination just what Dr. Kuttner stated, namely, very little fluid but marked dilatation of the heart to account for the congestion. That was our diagnosis in this case, and we attempted treatment of the heart failure without success.

Clinical Diagnoses

Rheumatic pericarditis.
Congestive failure.

Dr. Kuttner's Diagnoses

Acute rheumatic fever.
Pericarditis, with bread-and-butter exudate and little or no effusion.
Rheumatic heart disease, with mitral regurgitation.

Anatomical Diagnoses

Acute rheumatic endocarditis, mitral and aortic.
Acute rheumatic myocarditis (Aschoff bodies).
Acute rheumatic pericarditis.
Cardiac hypertrophy and dilatation.
"Rheumatic pneumonia."
Petechial hemorrhages of pleura, peritoneum and pericardium.

Pathological Discussion

Dr. Castleman: The autopsy showed an enlarged heart, weighing 330 gm., which was certainly over twice the normal weight for a child of this age. There was a bread-and-butter type of pericarditis, with large masses of shaggy fibrin and organizing exudate and little fluid. There were also petechial hemorrhages in the pericardium, and a hemorrhagic focus in the myocardium.

Microscopic examination of numerous sections of the heart showed a severe rheumatic myocarditis, with areas of acute degeneration of the myocardial fibers, foci of polymorphonuclear infiltration and numerous characteristic Aschoff nodules in the adventitia of the blood vessels. The endocarditis was acute, involving both the mitral and aortic valves, without any evidence of an older process, such as interadherence of the aortic cusps or shortening or thickening of the chordae tendineae of the mitral valve. There were petechial hemorrhages in the pleura and peritoneum, which is a frequent finding in acute rheumatic infection.

The lungs also showed numerous hemorrhagic foci and were markedly edematous. On microscopic examination some of the alveoli were filled with polymorphonuclears, others with red blood cells, and most of them contained large monocytes. Many of the alveolar sacs and respiratory bronchioles were lined with a pinkish-red hyaline membrane. Both the gross and microscopic findings are characteristic of what is often called "rheumatic pneumonia," although these findings are certainly not specific for rheumatic fever. The hyaline membrane is seen in other conditions, such as influenzal pneumonia, and Dr. Farber[3] has frequently found it in newborn infants after aspiration of the contents of the amniotic sac. He and Wilson[4] showed that it could be produced experimentally when air and a foreign substance, such as exudate in the lung, came in contact with each other. An excellent review of the whole subject of rheumatic pneumonia has recently been published by Epstein and Greenspan,[5] who found this hyaline membrane in 50 per cent of the patients dying in their first attack of rheumatic fever.

References

1. Massell, B. F., and Jones, T. D. Effect of sulfanilamide on rheumatic fever and chorea. *New Eng. J. Med.* 218:876-878, 1938.
2. Swift, H. F., Moen, J. K., and Hirst, G. K. Action of sulfanilamide in rheumatic fever. *J. A. M. A.* 110:426-434, 1938.
3. Farber, S., and Wilson, J. L. Hyaline membrane in lungs. I. Descriptive study. *Arch. Path.* 14:437-449, 1932.
4. *Idem.* Hyaline membrane in lungs. II. Experimental study. *Arch. Path.* 14:450-460, 1932.
5. Epstein, E. Z., and Greenspan, E. B. Rheumatic pneumonia. *Arch. Int. Med.* 68:1074-1094, 1941.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*

James P. O'Hare, M.D. — William B. Breed, M.D.
Conrad Wesselhoeft, M.D. — Oliver Cope, M.D.

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

EDITORIAL BOARD

Joseph Garland, M.D. — A. Warren Stearns, M.D.
Shields Warren, M.D. — Dwight O'Hara, M.D.
C. Guy Lane, M.D. — Chester S. Keefer, M.D.
William A. Rogers, M.D. — Howard M. Clute, M.D.
Stephen Rushmore, M.D. — Fletcher H. Colby, M.D.
Henry R. Viets, M.D. — Robert L. Goodale, M.D.
Robert M. Green, M.D. — Chester M. Jones, M.D.
Charles C. Lund, M.D. — Harvey R. Morrison, M.D.

ASSOCIATE EDITORS

Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., EDITOR EMERITUS
Robert N. Nye, M.D., MANAGING EDITOR
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year, Boston funds; $8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Friday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

STANDING ORDERS FOR NURSES IN INDUSTRY

THERE has probably never been a more appropriate time than the present to discuss medico-nursing relations in industry, in public health or in any of the fields where the physician and the nurse obtain their best results by co-operative effort. The functions of these two professions should be integrated without gaps and without overlapping if the best service to the patient is to be devised and delivered.

Standing orders have long been applied and highly developed in hospital practice. In the home of the patient, private practice has usually patterned itself on hospital precedent, although frequent modifications of hospital concepts have naturally accompanied the easier discipline of home environments. The Massachusetts Department of Public Health has recently issued a mimeographed pamphlet containing suggestions for standing orders to guide public-health nurses in their community visits, and the Council on Industrial Health of the American Medical Association has likewise formulated a set of standing orders for nurses in industry, which was published in the August 28 issue of the *Journal of the American Medical Association*.

These all strive to codify the behavior, in each profession, of those who are not only well trained but who possess good moral perspective. If all doctors and nurses could be endowed with these attributes, codes and formulas would become relatively simple and perhaps unnecessary; but most of us are imperfect, and all of us find ourselves confronted with situations in which it is at least reassuring to have a rule to follow.

The report of the Council on Industrial Health is especially useful for those in its field, for it not only indicates that there must be advance planning in relation to emergencies of all sorts, but it discusses the questions raised by nonoccupational illness, pregnancy and minor complaints. All these have a more or less direct relation to private medical practice, and frequently call for tact and discernment in the industrial medical department. Appended to this report is a list of references to recent publications and textbooks.

The report makes one general observation that will be much to the point in many industrial establishments: namely, "The greater the amount of personal supervision exercised by the physician directly in the industrial environment, the better is the industrial health service." Too frequently the nurse is expected to carry the entire responsibility, except in the case of serious accidents, and the physician is involved only when he is called on a fee basis and for a specific need. This code of standing orders is a good starting point from which such a plan can step into the line of progress now forming in the field of industrial health.

CURTAINS FOR RAW MILK

THE newly adopted regulation of the Boston Health Department that put an end to the sale of raw milk in the city as of September 30, 1943, is another, and an impressive, milestone in the progress that has been made over the years in the production and distribution of safe milk.

The road has been a long one. In 1893 the first important step in the production of clean milk was taken in Newark, New Jersey, when Dr. Henry L. Coit formulated the idea of certified milk, and put in into execution. The Legislature, about 1895, established a compulsory tuberculin test for cattle throughout Massachusetts. The slaughter was so great that the act had to be repealed, to save the farmers, if not the children. In 1906, risking considerable criticism, the State Board of Health initiated the first systematic dairy inspection. From then on improvement was slow, but steady, under a succession of able state and city health commissioners, with alert medical milk commissions watching over the production of certified milk.

During the term of office of the late Dr. Francis X. Mahoney as health commissioner of Boston, the sale of all raw milk in the city, unless certified by the Boston Medical Milk Commission, was prohibited. In 1930, the commission, against the opposition of its parent organization, the American Association of Medical Milk Commissions, put through the permissive pasteurization of milk on farms under its certification. The new regulation, that of universal pasteurization of all milk coming under the jurisdiction of the Boston Health Department, has been the constant aim of the present health commissioner, Dr. G. Lynde Gately, and the present milk inspector, Mr. Frank E. Mott, as it had been of their predecessors in office. Such a goal could be achieved only through education of, first, the medical profession, second, the milk producers and distributors, and third, the public. It is a source of gratification to the profession that the Boston Medical Milk Commission has been actively working toward this end.

Eventually, we may hope, the influence of this local achievement will help in the elimination of raw milk throughout Massachusetts and in the other states. We may also hope that expediency will not lead the federal authorities to experiment too far in streamlining the production and grading of milk. Too much time and effort have been put into the development of superior grades of milk to have them swept aside by the stroke of a bureaucratic pen.

MEDICAL EPONYM

KAPOSI'S DISEASE

Moritz Kaposi (1837–1902) described the lesions of this disease in an article "Idiopathisches multiples Pigmentsarkom der Haut [Idiopathic Multiple Sarcoma of the Skin]" which appeared in *Archiv für Dermatologie und Syphilis* (**4**: 265–273, 1872). A portion of the translation follows:

> Without known cause, general or local, there develop in the skin brownish-red or bluish-red nodules, spotty, pea-sized or as large as hazelnuts. The surface is smooth, the consistence firm and elastic, often turgid, like a fungus haematodes. They may be solitary, in which case when they have grown larger, they protrude like bullets, or they may be grouped and remain flatter. In the latter case the central nodules of the plaque coalesce and give rise to a scar-like, darkly pigmented depression. They regularly appear first on the soles and on the dorsums of the feet, soon after on the hands as well; they also develop there most abundantly, for the most part, and are coupled with diffuse thickening of the skin and disfiguring of the hands and feet. . . .
>
> Finally, similar nodules form in the mucous membrane of the larynx, the trachea, the stomach, the intestine, being especially abundant in the large bowel down as far as the anus, and the liver.
>
> The disease is rapidly fatal, leading to death within a period of two or three years.

R. W. B.

CORRESPONDENCE

NEED FOR AVAILABLE PHYSICIANS

To the Editor: In a further effort to obtain for the armed forces those doctors who can pass a physical examination and who are marked available, I have written and signed the enclosed personal letter to every physician marked available in Massachusetts and New York and will shortly send the same personally signed letter to every such doctor in Maine, New Hampshire, Vermont, Rhode Island and Connecticut. A similar letter will eventually be sent to every doctor marked available in every state of the United States.

As stated in the letter each one of these doctors will receive a request to confer with a group visiting each state made up of representatives of the Army, the Navy,

Public Health Service and Procurement and Assignment Service.

It is my hope that this personal letter will serve to convince the doctors marked available that there is a real need for them to seek a commission in either the Army, the Navy, the Coast Guard or the Public Health Service.

FRANK H. LAHEY, M.D.
Chairman of the Directing Board

War Manpower Commission
Procurement and Assignment Service
Washington, D. C.

War Manpower Commission

PROCUREMENT AND ASSIGNMENT SERVICE FOR PHYSICIANS, DENTISTS, AND VETERINARIANS

Dear Doctor ———:

I am writing you a personal letter — personal because I do not want it to be taken as a form letter from the Procurement and Assignment Service. I want it to be personal in order that I may convince you that the Army, the Navy, the Coast Guard and the Public Health Service need more doctors. The Navy in terms of its requirements is farther away from what it needs than any other branch of the armed services but we need also to supply more doctors to the Army, the Coast Guard and the Public Health Service. Every doctor who has been marked available should either seek a commission or appeal his classification.

You, as a physician of forty-five or under who has been marked available, will shortly receive a notice asking you to appear for a conference with a group made up of representatives of the Army, Navy, Public Health Service and Procurement and Assignment Service. This group will be able and willing to discuss with you any questions that may be in your mind concerning entering the service and applying for a commission.

I wish to give you my personal word that the Directing Board for the Procurement and Assignment Service assures you, one, that those doctors marked available who can pass the physical examination are needed, and two, that they can be spared where marked available without interfering with civilian care.

In the interests of the national need, will you not at least appear before this board as a man marked available to discuss the problem as it relates to you?

I am certain that you know that I would not write this personal letter unless the need was real and my conviction of its justice established.

Sincerely yours,
(Signed) Frank H. Lahey
FRANK H. LAHEY, M.D.
Chairman of the Directing Board

NOTICES

GREATER BOSTON MEDICAL SOCIETY

A dinner meeting of the Greater Boston Medical Society will be held at the University Club on Wednesday, November 17, at 7 p.m. Mr. William Gailmor, news commentator, Station WHN in New York City, and lecturer and propaganda analyst, will speak on the subject, "Russia's Role in a Postwar World." As an added feature, Lieutenant Commander David B. Stearns, U.S.N.R., will give a short talk entitled, "A Urologist at a Naval Air Station."

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 16, at twelve noon. Dr. Henry C. Marble will speak on the subject, "The Care of the Wound."

Physicians are cordially invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore on Wednesday, November 17, at 8 p.m. Dr. William D. McFee will act as chairman.

PROGRAM

Fundamentals in Teaching Galvanic Technic. Dr. Harry E. Stewart, president, Junior College of Physical Therapy, New Haven, Connecticut, and chairman, Section of Physical Therapy, Connecticut State Medical Society.

Ionization. Dr. Wilmot L. Marden.

A council meeting will be held at 6 p.m., and dinner in the Empire Room at 6:30 p.m.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held in the Boston Medical Library on Monday, November 29, at 8:15 p.m.

PROGRAM

Observations on Re-examination of Men Rejected for Military Service for Cardiovascular Reasons. Dr. Paul D. White. Discussion by Drs. Burton E. Hamilton, Henry Jackson, Jr., and Samuel A. Levine.

Report of a Patient with Eisenmenger's Syndrome. Drs. C. Sidney Burwell and Eugene C. Eppinger.

Circulation and Respiration During an Episode of Chill and Fever in Man. Drs. Mark D. Altschule, A. Stone Freedberg and Haim Haimovici.

Notes on the Transmission of Cardiac Murmurs. Dr. Samuel A. Levine.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The regular fall meeting of the New England Oto-Laryngological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Wednesday, November 17.

PROGRAM

10 a.m.–12 m. Sound Motion Pictures (Mosher Laboratory).

2 p.m. Clinical meeting. Presentation of cases from the Massachusetts Eye and Ear Infirmary.

3 p.m.

Business meeting.

Two Instruments of Value in Tonsillectomy. Dr. Henry H. Amsden, Concord, New Hampshire.

The Significance of Eosinophilia in Rhinology. Dr. Daniel Miller.

(Continued on page x)

New . . .

an aqueous chloramine solution with a surface tension of 30 dynes/cm.

Surface Active Saline Mixture of AZOCHLORAMID, W&T

REG. U.S. PAT. OFF.

From their inception, AZOCHLORAMID* preparations have been recognized as possessing a distinctively low chlorine potential, and as a consequence, are nonselectively bactericidal over prolonged periods as well as being non-toxic and virtually non-irritating.

This new Azochloramid preparation provides further clinical effectiveness through the addition of the highly surface-active compound—sodium tetradecyl sulfate. This unusually effective wetting agent reduces the surface tension of the aqueous solution from 72 dynes/cm. to 30 dynes/cm.

Thus it will penetrate otherwise inaccessible areas such as the many crypts and recesses commonly making up the greater part of a contaminated or infected wound. It is an excellent agent for the liquefaction and dispersion of pus and other types of organic débris in wound surfaces or cavities.

Clinical reports attest the value of solution of Surface Active Saline Mixture of Azochloramid as a lavage during surgical débridement, for irrigations and instillations, for wet dressings, and for hot compresses. Available in powder form in bottles to prepare 1 gallon or 25 gallons of aqueous solution at hospital and prescription pharmacies.

*Chloroazodin U. S. P.

ARMY E NAVY

BUY BONDS

For detailed literature and samples write to
WALLACE & TIERNAN PRODUCTS, INC., P. O. BOX 178, NEWARK 1, NEW JERSEY

WALLACE & TIERNAN PRODUCTS, INC.
Belleville, New Jersey, U.S.A.

W&T

Extranasal Block Anesthesia for Submucous Resection of the Nasal Septum. Dr. Gustave B. Fred.
Case of Osteomyelitis and Frontal Lobe Abscess with Recovery. Dr. Jost J. Michelsen.
Experiences with Resection of the Cervical Esophagus. Dr. Richard H. Sweet.
Relation of the Nose and Throat to Poliomyelitis. Dr. William Lloyd Aycock. Discussion by Dr. Conrad Wesselhoeft and Dr. Harris P. Mosher.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 18

THURSDAY, NOVEMBER 18
•9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

(Continued on page xiii)

J. S. WATERMAN & SONS
SINCE 1832
FUNERAL SERVICE
Local and Suburban

Prescribe
FERROSATE
It speeds up hemoglobin reticulocyte formation
Bottles of 100 4-gr. tablets sold everywhere
Free sample on request
Kenmore Pharmacy, Inc.
500 Commonwealth Avenue, Boston, Mass.

What to Tell Your Patients about KARO in Wartime

The exigencies of wartime production have not affected the purity, quality and effectiveness of KARO as a milk modifier.

However, some grocers may be temporarily short of either *Red* label or *Blue* label KARO.

Since *both* types *are* practically identical in dextrin, maltose and dextrose content, *either may be used* in all milk mixtures. The slight difference in flavor in no way affects KARO's essential value for prematures, newborns and infants.

How much KARO for Infant Formulas?

The amount of KARO prescribed is 6 to 8% of the total quantity of milk used in the formula—one ounce of KARO in the newborn's formula is gradually increased to two ounces at six months.

CORN PRODUCTS REFINING CO.
17 Battery Place • New York, N. Y.

FRIDAY, NOVEMBER 19
*9:00–10:00 a.m. Medical Treatment of Hyperthyroidism. Dr. E. B. Astwood. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, NOVEMBER 20
*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, NOVEMBER 22
*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 23
*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department. Massachusetts General Hospital.

WEDNESDAY, NOVEMBER 24
*9:00–10.00 a.m. Management of Uterine Fibroids. Dr. Louis E. Phaneuf. Joseph H. Pratt Diagnostic Hospital.
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

NOVEMBER 16. South End Medical Club. Page 766.
NOVEMBER 17. New England Society of Physical Medicine. Page 766.
NOVEMBER 17. New England Oto-Laryngological Society. Page 766.
NOVEMBER 17. Greater Boston Medical Society. Page 766.
NOVEMBER 29. New England Heart Association. Page 766.
DECEMBER 2. Boston Gastroenterological Society. Page xii, issue of November 4.
DECEMBER 9. Treatment of Allergy. Dr. Francis M. Rackemann. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
FEBRUARY 12. American Board of Obstetrics and Gynecology. Page ix, issue of October 28.

DISTRICT MEDICAL SOCIETIES

SUFFOLK
DECEMBER 2. Censors' meeting. Page x, issue of September 16.

WORCESTER
DECEMBER 8. Worcester City Hospital.
JANUARY 12. Memorial Hospital, Worcester.
FEBRUARY 9. Worcester State Hospital, Worcester.
MARCH 8. St. Vincent Hospital, Worcester.
APRIL 12. Hahnemann Hospital, Worcester.
MAY 10. Annual Meeting.

BABIES THRIVE ON

Baker's

MODIFIED MILK

For both premature and full-term infants with or in place of breast milk at birth and during the bottle-feeding period. The liquid and powder forms, when prepared and diluted to normal strength, have the same analysis and can be fed interchangeably. Easy to use (dilute to feeding strength with cool water, previously boiled). Feeding instructions supplied to physicians only. Advertised only to the medical profession.

ACCEPTED AMERICAN MEDICAL ASSN. Council on Foods

The Baker Laboratories

Barre, Massachusetts

Channing Sanitarium

ESTABLISHED 1879

A pleasant country community of cottages built for the homelike care and treatment of nervous patients. Separate cottage for the care of convalescent nonmental patients. Occupational therapy. Tennis court. Sports building.

JACKSON M. THOMAS, M.D. *Superintendent* CLIFFORD G. ROUNSEFELL, M.D. *Resident Physician*

WELLESLEY, MASSACHUSETTS

Telephone — Wellesley 0464

BREAST MILK

may be obtained at the offices and laboratory of

The

Directory for Mothers' Milk

Incorporated

221 Longwood Avenue, Boston
Telephone BEA 5330

Prices will be adjusted to make the milk available to all who need it

Sent packed in ice to all parts of New England

Bournewood Hospital

300 SOUTH STREET, BROOKLINE, MASS.

Established 1884

For a limited number of cases of mental and nervous diseases

POST OFFICE, CHESTNUT HILL

Telephone PAR 0300

GEORGE H. TORNEY, M.D.

Washingtonian Hospital

41 WALTHAM STREET, BOSTON, MASS.
Founded 1841

A non-profit-making, endowed institution, reorganized, for the

MODERN TREATMENT OF MEN SUFFERING FROM ACUTE OR CHRONIC

ALCOHOLISM

JOSEPH THIMANN, M.D., *Medical Superintendent*
MERRILL MOORE, M.D., *Director of Research*

Visits by Psychiatric and Neurological Staff
Consultants in Medicine, Surgery and the Specialties
Rates Moderate
For information: consult the Medical Superintendent
Telephones: HAN 1750 and 1751

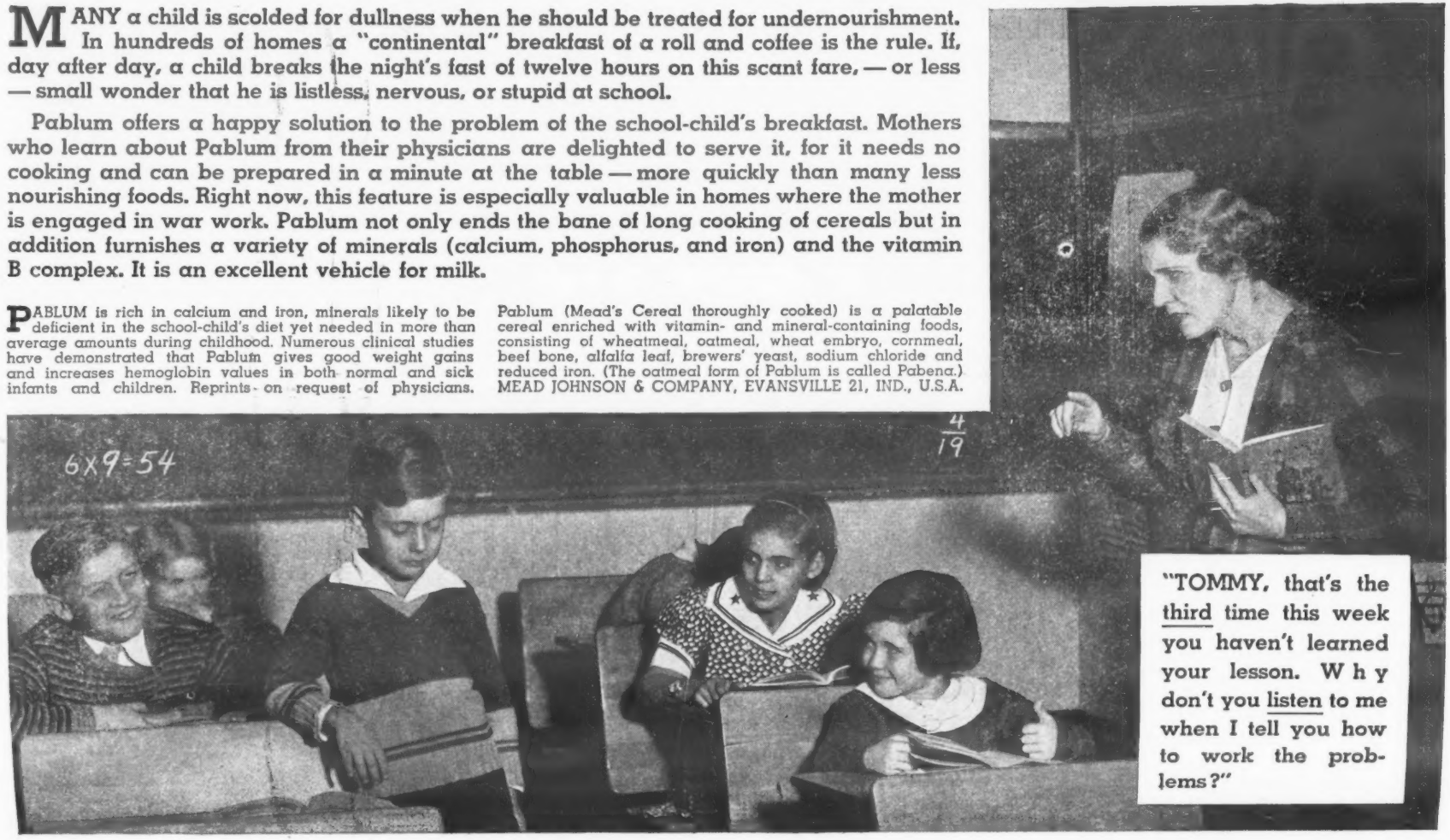
a Poor Scholar . . . because of a Poor Breakfast

MANY a child is scolded for dullness when he should be treated for undernourishment. In hundreds of homes a "continental" breakfast of a roll and coffee is the rule. If, day after day, a child breaks the night's fast of twelve hours on this scant fare, — or less — small wonder that he is listless, nervous, or stupid at school.

Pablum offers a happy solution to the problem of the school-child's breakfast. Mothers who learn about Pablum from their physicians are delighted to serve it, for it needs no cooking and can be prepared in a minute at the table — more quickly than many less nourishing foods. Right now, this feature is especially valuable in homes where the mother is engaged in war work. Pablum not only ends the bane of long cooking of cereals but in addition furnishes a variety of minerals (calcium, phosphorus, and iron) and the vitamin B complex. It is an excellent vehicle for milk.

PABLUM is rich in calcium and iron, minerals likely to be deficient in the school-child's diet yet needed in more than average amounts during childhood. Numerous clinical studies have demonstrated that Pablum gives good weight gains and increases hemoglobin values in both normal and sick infants and children. Reprints on request of physicians.

Pablum (Mead's Cereal thoroughly cooked) is a palatable cereal enriched with vitamin- and mineral-containing foods, consisting of wheatmeal, oatmeal, wheat embryo, cornmeal, beef bone, alfalfa leaf, brewers' yeast, sodium chloride and reduced iron. (The oatmeal form of Pablum is called Pabena.)
MEAD JOHNSON & COMPANY, EVANSVILLE 21, IND., U.S.A.



"TOMMY, that's the third time this week you haven't learned your lesson. W h y don't you listen to me when I tell you how to work the problems?"